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Editorial

The position of fundamental age studies

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The concern of scientists—as against mystics, quacks, and therapeutic optimists—with the control of human age processes, if we date it to Metchnikoff and Claude Bernard, is less than a hundred years old; the engagement of science in studying it as an immediately realizable project is less than ten. Gerontology in its modern sense dates from about 1950.

In these ten years its advocates have generated a large body of printed matter, set up many institutes, and held many conferences, from which, so far as the fundamental understanding and control of age processes are concerned, virtually nothing hard emerges which could be put honestly to a lay committee as evidence of "definite progress." The view of some sources of research money that gerontology has now deservedly talked itself out of work is therefore comprehensible: but this ignores the time which is required, in any pioneer project, to be spent in cutting brushwood and reclaiming ground before a crop of fundamental experiments can be sown, let alone harvested. Though some of the time and effort spent so far has been wasted, a certain amount has been achieved in defining the problem, clearing old errors, raising a generation which knows the possibilities and difficulties of age research, and discharging various ill-judged or superficial ideas which would have had to be voided at some point. Accordingly, although it has borne no fruit yet in medicine, the work done may later prove more important than it now appears to be.

The root questions which determine the form of the age problem remain much as they were in 1950. In man and other warm-blooded vertebrates, vigor declines and disease-susceptibility multiplies with increasing age. The rate of this increase under the best conditions has a characteristic value in each species, and is exponential, so that there is a maximum practicable life span which further betterment does not lengthen.

Mammals are made up of three biologic components: cells multiplying clonally throughout life (white corpuscles, epithelial cells), cells incapable of division and renewal (neurons), and noncellular material which may have much or little turnover (collagen, intercellular substance). There are, accordingly, three grand classic hypotheses of the mechanism of senescence (not necessarily mutually exclusive), which must at some stage be dealt with—that vigor declines through change (epigenetic, mutational, infective, immunological) in the properties of multiplying cells; that it declines through loss of, or injury to,

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nonmultiplying cells; and that it declines through primary changes in the "inert" materials of the body. All these are old hypotheses dating from Francis Bacon; none has yet been investigated by convincing experiment. At present, interest in mutation and in matters such as somatic aneuploidy has focused attention on the first hypothesis—that new cells in old animals are not so good as new cells in young animals. Szilard's recent speculations[48,49] fit better to the second hypothesis—that irreplaceable cells are lost with time. The third hypothesis has generated extensive and important work on collagen and related substances—this is probably the only branch of gerontology widely known to physicians; for that reason it will not be summarized here.

One preliminary of any choice between these possibilities has been the need to observe the aging and age-mortality relationship of animals other than men and rodents (which until recently were the only mammals for which we had life tables), and the study of factors which appear to hasten or delay the decline of vigor. This has been begun, though slowly. Another requirement is the detailed study of cell populations and numbers at different points in the life cycle; a third is the comparison of the new cells of old animals with those of young animals. None of these has yet been adequately attacked. The decline of brain-cell population at various ages in man,[10,55] guinea pig,[52] rat,[24] and even the honey bee,[35,36,40,46,51] and termite[22] has been very variously estimated, whereas histochemical studies of old and young animals still frequently fail to distinguish between young cells in an old organism and cells which are themselves old[3]—or between animals such as rotifers, nematodes, and insect imagos, in which there is no cell division, or little, and mammals in which fixed and endlessly dividing cells exist together.

Throughout its history the study of aging has been ruinously obscured by theory, and particularly theory of a type which begets no experimental hypotheses. The discussion of methods which has taken place, and which has been quantitatively the main activity of gerontology so far, has been worth while in laying some of these ghosts, and though it is depressing to see them being raised again from time to time by the darkeners of scientific counsel,[37] the most important recent contributions to theory, such as Szilard's stochastic and Burnet's immunologic speculations, all carry direct experimental consequences. It is noticeable that most of these theories have come from experimenters of international stature who are themselves working in other fields; serious progress in experimentation on age processes is really now waiting for some experimenter of equal caliber to devote his whole time to it.

It will be necessary here to discuss three theories, all of which have been contributed in this way—leaving aside the contribution of information theory, which at present records only established actuarial theory, though in a form which may prove instructive in the end. Thus, though the difference in life span between species can be treated as a difference in initial information content,[43,56] we are no nearer translating this into material terms. Even though none of these seems likely in itself to "explain" aging, they merit close attention as evidence of the way in which aging research and control have come to present themselves in practical terms to scientists of high ability, and it is this fact, rather than the theories themselves, which makes it possible that fundamental progress in the understanding of the loss of vigor with aging may be closer than the standard of experimental papers might lead us to think. Of course, understanding and control are very different things, and the medical relevance of understanding the age process will depend upon what we understand it to be.

Vertebrate vital statistics

Some choice between hypotheses of aging might be made by comparing the shape of the age-mortality function with other characters of the life cycle, but not so long as man and rodents were the only available source of vertebrate vital statistics. Some of the difficulties of getting this kind of information in sufficient quantity and quality have been described elsewhere[11,12]: figures have eventually been forthcoming for dogs[14] and horses[13] and

for small series of ruminants in zoos[12] from existing records, and a lifetime study of beagles is now being undertaken[50] as a by-product of radiation research, where the interrelation of life span, body size, and cell number has become a critical issue in determining the percentage decrease in longevity per rem.[34] There are still no proper figures for birds under protected conditions, or for cold-blooded vertebrates, but a laboratory study of an experimental fish[16] population has failed to support Bidder's conjecture,[2] that animals of indeterminate growth should not age: the age-dependent mortality of a small fish (Lebistes) behaves almost exactly like that of a rodent. It remains to be established how far the much longer lives of fish and reptiles, compared with mammals of similar size, are the result of longer sustained or more extensive cell-replacement: they might imply lower vulnerability to copying faults at lower chromosome numbers.

Fresh theoretical attempts have been made to relate the time scale of aging to other factors, such as size—the closest correlate seems to be the index of cephalization,[42] i.e., the excess of relative brain weight over the average for all mammals. This relationship holds good both between species—though admittedly upon inadequately characterized data for "life span"—and, in dogs, between big and small breeds within a species,[14] but the significance of it is obscure.

Factors modifying the age-dependent increase in mortality

Underfeeding. McCay's original observation[29-31] that rats can be made to live twice as long as usual by severe but controlled underfeeding remains a key finding which has been little if at all elucidated in thirty years. It is still not clear whether continued growth, postponement of differentiation, or a specific damage effect of high intake of food is responsible.

The literature of life-prolongation by underfeeding has been recently reviewed[15,47]: in a great many animals, from suctorians[41] and cockroaches[2] to rodents, the optimal intake of food for growth is not the optimal for longevity. In rats and mice, at least two effects seem to be present—a reduction of disease with sparer diet, and an actual postponement of development, including senescence: the effects of mild restriction probably represent the first, and of severe restriction the second. Rats which receive a diet adequate in all but calories can be kept immature and strikingly free of the diseases which affect full-fed litter mates. After restriction in this way for periods up to 1,000 days the survivors were able to resume growth, mature sexually, and live, in all, substantially longer than controls. The gain in further expectation was not equal to the period of restriction, and was greater in males than in females. The retarded rats were active but immature[1,53]: in early experiments the main finding was that members of each retarded group were still alive after all controls had died, and the gain in life span was limited to the survivors of a substantial early mortality, but the aggregate curves based on later experiments[45] show definite lengthening of the adult "plateau" and displacement of the modal age of death.

In Wistar rats the gain in life is roughly proportional to the severity of the underfeeding—starvation for one day in three or four produced a significant increase in mean life.[38] The gain was greater on an omnivorous than a vegetarian diet.[7] By a fast of one day in three, the mean expectation can be increased by 20 per cent in males and 15 per cent in females, without arrest of growth.[6]

Experiments in mice have given very similar results. Both total and reproductive life are increased by restriction of calories. On a diet which contained half the calories (as lard and dextrose) in the standard diet, C3H females which are normally sterile at 11-12 months were still breeding at 21 months.[8] A fast of two days out of seven, with or without the addition of nucleic acid to the diet, produced an increase of 50 to 60 per cent in the life of albinos.[39] There is also a large literature of the special effects of limiting particular dietary ingredients in particular strains.[47]

It is still not possible to relate these observations clearly to the causation of aging in rodents. The operative effect of underfeeding seems to be a "dietary hypophysectomy."[23] The apparent youth of underfed rats extends to the contractility

of their tail collagen, which remains "young" in pattern[9]; it has been claimed that their cells have a shorter latent period in tissue culture than that of controls.[21] Dietary size-limitation depends upon a smaller cell number; retarded animals have the cell-population appropriate to size group, not age group.[19] At the same time, their irreplaceable cells may be "protected," as judged from the reduction in degenerative disease, though basal metabolism is significantly higher than in unrestricted age-mates.[53] Fundamental research is badly needed to interpret these observations in terms of aging theory.

Radiation. It is not yet clear whether the involvement of age studies with radiation biology will prove to be the key to the nature of aging or a mischievous diversion of energy—it has at least focused on age processes the attention of workers who would not have examined them otherwise, and has induced them to set up long-term studies. Exposure to ionizing radiation shortens life. It differs from the many other agents which do this in the close resemblance between its effects and the natural loss of vigor due to aging, which it appears to accelerate. In exposed rodents a single exposure in early life produces a loss of expectation equivalent to a jump forward in age, the slope of the decline in the exposed population running parallel to, but earlier than, that in controls, in linear proportion to the dose: life-long exposure from birth produces a scalar contraction of the whole survival curve.[44] The important question for age studies is whether this shortening represents an acceleration of the process or changes which normally induce loss of vigor, whether it reduces vigor by some other, unrelated changes, or whether, like noise or exposure to traffic risks, it is simply an addition to the environmental attack rate. If radiation hastens normal aging, it should cause the failure of homeostasis to appear earlier in life, without affecting its form, and the exposed animals should die at younger ages than the controls, but of the same diseases in the same sequence. In the biggest and most recent study of one-shot irradiation applied to mice, Lindop and Rotblat[26-28] carried out detailed postmortems on all the animals; they found that although the survival curve is moved toward the origin in a way which indicates a decrement in "vigor," the order of diseases in irradiated and control animals is not identical, and the action of radiation is, therefore, presumably not a simple moving forward of the normal age process.

Theories

Germane to the interest of radiation biologists in aging, and age biologists in radiation, are three theoretical suggestions, all unproved, all open to various objections, but all intelligent and original enough to be regarded as significant. The first is simply the idea that the predominant process in aging is somatic mutation, leading to changes in the properties of clonally dividing cells and loss of capacity in fixed postmitotics. Its cause would be the sum of mutagenic influences on the body, and if radiation accelerated aging, it would do so, in part at least, by increasing the mutation rate.[18] The first suggestion of this in the literature seems to be that of Kunze,[25] who put it down to cosmic rays. In putting it forward again Failla points out that the large discrepancy between the observed and calculated "background equivalent" dose in irradiated mice can be removed if we allow for exposure to "background" in prenatal life, when radiation sensitivity is substantially higher. Failla is the originator of the term "hit" to describe a hypothetical lesion—point mutation, chromosome loss, or other—occurring in a cell and inactivating it. The term has been taken further in the elaborate stochastic model devised by Szilard.[48,49]

Szilard assumes that the elementary step in aging is a "hit" (not necessarily by a radiant particle) which renders inactive all the genes on one chromosome of a somatic cell. "Hits" are random events; the probability of any one chromsome being hit remains constant throughout life, and the over-all rate of occurrence of hits is characteristic of the species. As a result of hits, the proportion f of adequately functioning somatic cells declines with time until it reaches f^*, at which point the probability of death within unit time (in man, one year) is unity.

At the same time, each individual is assumed to carry a load of genetic "faults."

A "fault" is a mutation in one of the genes essential to the proper working of a somatic cell. Szilard assumes that the number of these genes in man is 3,000 out of a probable total of 15,000. A cell becomes inoperative when both of the pair of any such genes are put out of action. Accordingly, when a chromosome receives a hit, the cell will cease to function (a) if the homologous chromosome has already also received a hit, or (b) if the homologous chromosome carries a "fault" at any point. By assuming probable values for several quantities which no one accurately knows, Szilard proceeds from this model to draw plausible approximations to quantities which are known, such as the concordance between twin ages at death. He also proposes not an experimental proof, but at least one critical experiment—the reduction of life span of the progeny of irradiated mice could support or negate the model.

The model itself has other interesting implications. One is that if m, the number of chromosome pairs, differs between species, the specific life shortening per rem will be greater for that in which m is the smaller, and vary inversely as $\sqrt{m}$. Szilard also works out, on the assumption of an average on $n = 2.5$ inherited faults per head for the human female, the modal longevity of a genetically perfect female with no such faults; it comes to 92 as against the present 80 years. If $n > 2.5$, it would be more.

Szilard's model is deeply ingenious, but for the biologist, as for the late Ernie Pyle, "the first word which comes to mind is But." Such simplified mathematical models can bring light to a subject—as did Morgan's assumption of the simple linearity of the genes—or merely darken it further. For the model to be relevant at all it seems essential that aging should be timed by a fault in replication following the loss of one allele in the cell. This raises two grave objections, pointed out at once by Maynard Smith[32] and met by Szilard only at the expense of new variables.[49] The first is that, if the fault-hit hypothesis is right, the life of homozygous and inbred animals should be longer than that of heterozygous and hybrid animals, whereas the reverse is almost universally true. The second is that the only reason for Szilard's assumption that a hit inactivates a whole chromosome appears to be the need to find a hittable object yielding the right order of magnitude to account for, e.g., the difference between male and female longevity, there being too many genes and too few cells to do so. It is also difficult to relate the whole model to the dynamics of cell division in a system which contains fixed and multiplying cells, where faults acquired by stem cells as the result of "hits" will be communicated to a varying cellular progeny. If the critical fraction f^* represents simply surviving cell number in general, it is difficult to credit either Failla's or Szilard's version of the cell-loss hypothesis, even if the effect of a "hit" is not necessarily the physical removal of the cell. Failla,[18] for example, assumes that "vitality" (the reciprocal of mortality) is $\propto f$, the proportion of effective cells remaining, so that

$$\frac{f^t}{f^0} = e^{-\alpha t} = \text{spontaneous mutation rate},$$

α being the slope factor of the Gompertz equation; and he points out that in this case the hitting process must damage rather than destroy the cell, as otherwise only 5.8 per cent of the cells alive in man at age of 35 would survive in him at the age of 65. Szilard's theory seems to give an almost equally high rate of cell loss, whereas both completely ignore the question of replacement. If, on the other hand, f^* represents a fraction, not of cell-number but only of an unspecified stuff "vitality," the further equations do no more than restate actuarial observation in new terms. To make them experimentally useful it would seem that aging must be timed by the loss of key postmitotics (possibly in a single organ) or by a process with the same mathematical shape. There is finally the difficulty common to all mutational theories of aging, that chemical mutagens do not seem to hasten it, or mimic the life-shortening effect of radiation.[17]

The third stochastic theory, by contrast with the Szilard-Failla model, places the emphasis specifically on the dividing cell, but on one particular clonal system. Antibodies are now thought to be produced by lymphocytes, and the acquired power of making a particular antibody appears to be transmitted by a lymphocyte to its

progeny. A mechanism, not fully understood, determines that lymphocytes shall not normally respond to their proprietor's body constituents by forming antibodies against them. Burnet[4] has suggested that if mutation in lymphocytes followed by selection determines the various reactive capacities which they show, and if one possible mutation is the loss of this negative specificity to homologous antigens, then the organism might be expected to face a steady increase in autoimmune reactions with the passage of time—reactions which might well be of precisely the polymorphic, diffuse, and variable type which characterizes the infirmities of loss of vigor in aging, whereas the statistical constancy of the mutation rate and/or the rate of occurrence of Szilardian "hits" would remain to provide the stability of the survival curve on which life assurance depends.

The revival of immunologic age theories is an unexpected return to Metchnikov,[33] who always predicted that the same cellular mechanism would prove to be morphogenetic in the embryo, defensive in the adult, and destructive in the end. Burnet's suggestion is open to experiment, and may possibly be confirmed or refuted reasonably quickly. Moreover, if true, it would mean that aging was likely to be much more accessible to medical interference than it is now prudent to expect. It is not incompatible with some aspects of the Szilard-Failla model—the effect of a hit in this case is not that it removes a cell from useful activity, but that it puts a cell and its progeny into harmful activity. Burnet's general theory of "clonal selection"[4] seems to imply that mutational instability in the lymphocyte system is used adaptively by the body, and moreover that the harmful mutation with loss of negative specificity also confers protection on the mutant against being "selected out" by normal body mechanisms, f^* being now no longer a cell balance below which we are bankrupt, but the fraction remaining after a lethal percentage of cells has become corrupted in this way. Burnet's theoretical argument persuasively urges that something of the sort ought to happen. What is now required is experimental evidence that it does so.

Conclusion

From what has been said, the position of "fundamental" age research, stated in less rarefied terms, is this: in spite of the lack of an inspired experimental "line" (if we except McCay's thirty-year-old work on rat longevity, which has still not been properly worked out in a manner which shows why underfeeding lengthens life), and in spite of the desultory character of the experimental and the speculative character of the theoretical papers which have appeared, we may well be within striking distance of a concise statement of the chief process in the loss of vigor due to aging in human beings. The main requirement for this is probably (unless we rely on luck) the full-time attention of one or more first-rate experimental talents. The minor requirement, which is certainly necessary, though it may not prove sufficient, is a detailed knowledge of the age trend in cell population, cell capability, and somatic cell variation—preferably in man, since the real motive of age studies is to control in human beings the changes due to aging. It has to be remembered that the medical target of the immediate clinical studies, e.g., on collagen or on vital capacity, and that of work on fundamental age biology are different. So are their probable consequences. Unless the single given pathologic change or process which we happen to select is a major time-keeping mechanism in man, successful clinical work on it will make more people die at ages distributed about the "specific age." This is the general tendency of medicine. *The aim of the biologic studies is to move the specific age itself, and the age-distribution of all age-dependent causes of death with it.* The possibility of doing this must depend upon whether we find that the general loss of vigor has an identity which can be attacked experimentally apart from its contributing parts: if, for example, the only unity in aging processes is that they depend on age-dependent changes in the intensity of natural selection,[54,57] acting on our ancestors, the decline in vigor is not fundamentally attackable and can only be dealt with piecemeal. Apart from the equally urgent need to study human development as a unity, there is no other immediate medical problem which so clearly illustrates

our need for a specific medical biology, and for a biologic orientation in our medical teaching—without it, clinical studies risk finding themselves taking their direction from a group of scientific ideas with which clinicians will themselves not normally be familiar.

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Clinical communications

The ineffectiveness of an inotropic agent, mephentermine (Wyamine), in the treatment of congestive heart failure

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The ability of mephentermine sulfate (Wyamine), a synthetic sympathomimetic amine, to augment strikingly the contractility of both nonfailing and failing canine hearts has been well documented.[1,2] This agent acts primarily to elevate the ventricular function curve, and to improve the efficiency of the dilated, failing heart; its effects on the systemic arterial bed are minimal.[1] The drug is apparently well absorbed from the gastrointestinal tract, and it apparently shows little toxicity.[3] In view of these properties it appeared to be an ideal agent for the treatment of clinical chronic congestive heart failure.

Four patients with chronic inactive rheumatic heart disease (three with mitral and one with aortic regurgitation), one patient with arteriosclerotic heart disease, and one with myocardial failure of unknown etiology were studied. All patients had required a low-salt diet, digitalis, and diuretics prior to hospitalization. The patients were studied in the hospital, with daily observations of: (1) their clinical status in regard to signs and symptoms of congestive heart failure, (2) body weight, and (3) sodium balance. Venous pressure was determined at frequent intervals. When congestive heart failure was present, as evidenced by increasing dyspnea, orthopnea, gain in weight, and a positive balance of sodium, oral Wyamine was administered in doses ranging from 25 to 500 mg. daily in divided doses. One patient received up to 200 mg. of Wyamine daily intramuscularly.

In no instance did the administration of the Wyamine appear to exert any beneficial effect on the congestive failure state. Two patients appeared to show slight worsening. Typical experiments are illustrated in Figs. 1 and 2. Two of the patients exhibited no side effects from the Wyamine, whereas the others showed nervousness, and one patient had a transient psychosis.

The positive inotropic action of Wyamine demonstrated in the experimental laboratory appeared to exceed that exerted by digitalis glycosides.[4] Therefore, the lack of clinical benefit resulting from the administration of the sympathomimetic amine was unexpected. It is possible that an effective dose level was not achieved, and that had higher doses been employed, clinical benefit would have been apparent. However, this

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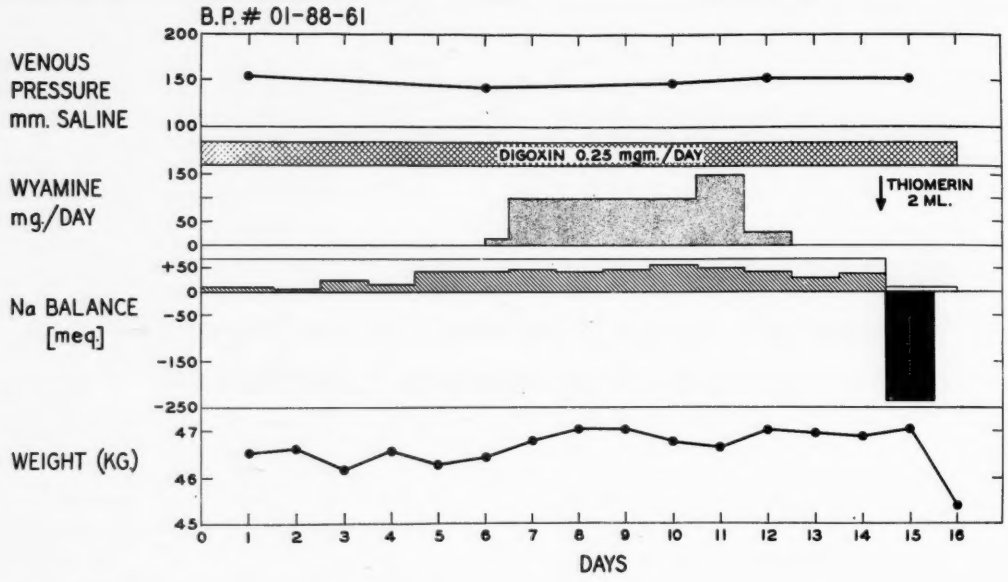

Fig. *1.* Observations on the effect of Wyamine in a patient with rheumatic heart disease, with mitral valve involvement and combined ventricular failure. The intake of sodium was held constant at 70 mEq. daily until the fifteenth day, on which it was lowered. The patient had moderate dyspnea and no change in his congestive failure state during the administration of Wyamine; the diuresis was induced with Thiomerin.

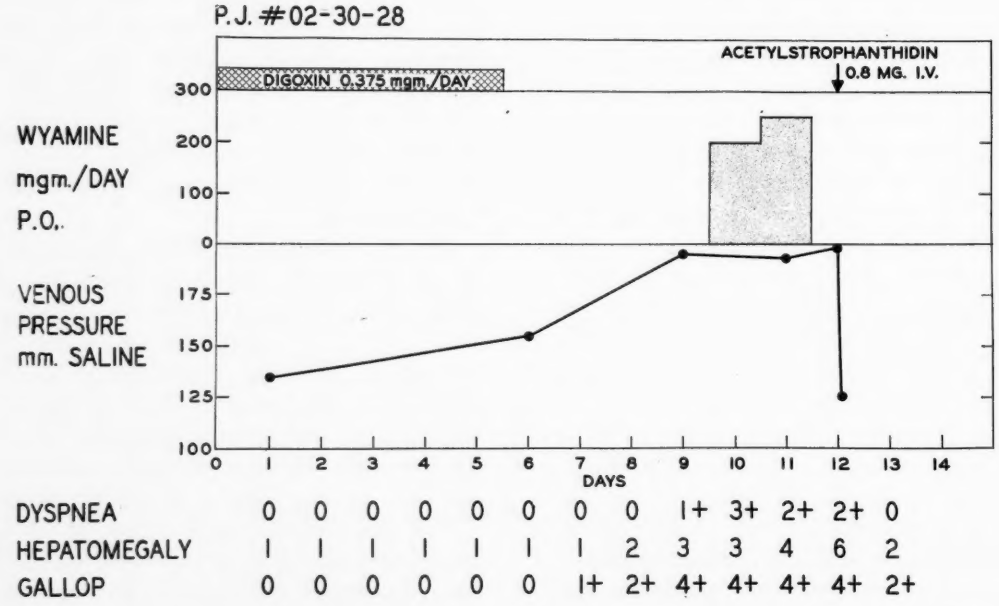

Fig. *2.* In this patient with rheumatic mitral regurgitation the symptoms and signs of heart failure appeared several days after digitoxin was discontinued. Failure progressed while Wyamine was administered, but promptly disappeared when he was given 0.8 mg. of acetyl strophanthidin. The severity of dyspnea and intensity of the gallop sound are graded on a scale from 0 to 4+, and the size of the liver is expressed in centimeters below the costal margin.

is unlikely since in two patients the heart failure actually became worse while they were receiving Wyamine. These observations emphasize that the state of clinical congestive heart failure is far more complex than the simple depression of myocardial contractility which may be induced acutely in the experimental laboratory, and which responds readily to treatment with sympathomimetic amines, and they would also

seem to underscore the clinical importance of treating the extracardiac manifestations of heart failure.

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A preliminary study of the electrocardiogram of the normal premature infant

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With recent advances in the diagnostic methods and surgical therapy for cardiac disease, cardiologists are now asked to evaluate younger and younger patients, even in the premature-infant age group. We soon came to realize that normal values have not been established for the electrocardiographic deflections and intervals of the premature infant. This preliminary study was designed to determine the range of normal of the several components of the electrocardiogram of the normal premature infant, in order to enable differentiation of the pathologic from the normal electrocardiographic record.

Material

A birth weight of less than 1,500 grams was considered to be evidence of significant prematurity, and was the criterion used for the admission of an infant to the study group. The seven infants studied were clinically well, with normal findings obtained on physical examinations at birth; the absence of cyanosis, cardiomegaly, congestive heart failure, and significant murmurs was specifically noted. A cardiac physical examination again confirmed the normal condition of the babies prior to their discharge from the hospital. X-ray examinations were not made. Follow-up physical examinations on a clinic basis were attempted after the infants were discharged from the hospital, in an effort to confirm the normal cardiovascular status. The results are shown in Table I.

Serial electrocardiograms were taken on these 7 premature infants, daily for the first week of life, three times during the second week, twice during the third week, and once a week thereafter until the infant had attained 2,000 grams, which is the requisite weight for discharge from the Grady Memorial Hospital Premature Nursery. In the infants studied, there was an essentially linear relationship between age and body weight. These seven infants varied from age 41 days to age 60 days at the time of discharge from the hospital. One hundred thirteen electrocardiographic records were thus obtained for analysis.

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Table I. *Follow-up examinations*

Patient	*Age at last examination*	*Cardiovascular examination*	*Comment*
1.	11 mo.	Normal	Well baby
2.	4 mo.	Normal	Moved out of Atlanta area
3.	3 mo.	Normal	Died suddenly at home 2 weeks after clinic visit—(aspiration?)
4.	13 mo.	Normal	Recurrent upper respiratory infections
5.	3 mo.	Transient soft apical systolic murmur—otherwise normal	Lost to follow-up
6.	2 mo.	Normal	Died suddenly at home 2 days after clinic visit—(aspiration?)
7.	10 mo.	Normal	Recurrent pneumonia

Method

Electrocardiograms were recorded at the standard paper speed of 25 mm. per second on the Sanborn Viso-Cardiette. The limb leads were recorded using standard extremity electrodes reduced in size to 2 × 3 cm. Since suction electrodes were impractical in these tiny infants, a standard electrode cut to 1.5 × 2 cm. and mounted on a cork for insulation from the operator's hand was used to record Leads V_1, V_2, V_4, V_6, and V_{3R} in the positions recommended by the American Heart Association. Alcohol sponges were used to reduce skin resistance. During the recording of the electrocardiogram the infants were in the supine position, with crying and kicking minimized by the use of a sugar-nipple pacifier. No sedation was administered at any time, and, indeed, the initial tracing was taken at least 8 hours after birth to obviate the effects of analgesia and anesthesia administered to the mother during labor. During the first week of life, electrocardiograms were obtained by inserting the electrode wires and the operator's hands through the ports of the Isolette, with oxygen and moisture being maintained as needed; later recordings were done in an infant bassinet. No attempt was made to establish any definite relationship of the recordings to feeding, time of day, temperature of the Isolette, etc. The body temperature of the infants varied from 93° to 100°F. during the course of the study, being partly influenced by the temperature of the Isolette.

The data obtained from the electrocardiograms of these premature infants were compared with the data of Ziegler[1] for the full-term infant of comparable age. The values cited for the full-term infant in all subsequent tables were reproduced from Ziegler's text with the kind permission of the author and publisher.

Data

The average *heart rate* (Table II) of these premature infants gradually increased from birth to 9 weeks of age (140 per minute to 176 per minute). This was similarly seen, but to a lesser extent, in the full-term infant, whose peak heart rate was observed at 1 to 3 months. Regular sinus rhythm was seen in all of our subjects, with no sinus arrhythmia or ectopic beats noted in any record.

The average *electrical axis of the P wave* for the entire age span studied was 40 degrees, decreasing from a mean of 55 degrees at birth to a mean of 35 degrees at 9 weeks of age. The P-wave electrical axis seemed to parallel the QRS axis in the premature infant (Fig. 1), whereas Ziegler found no relationship between the P-wave and QRS electrical axes in the full-term infant. As Ziegler observed in the full-term infant, the greatest P-wave amplitude was seen in Lead II. However, the absolute P-wave amplitude was greater for the premature than for the full-term infant in all leads. In the premature infants studied the P-wave amplitude was unrelated to age. There was no correlation between the P-wave duration (Fig. 2), which remained relatively constant, and the age or heart rate. Greater P-wave negativity was seen in Leads V_1 and V_2 in the earlier weeks of

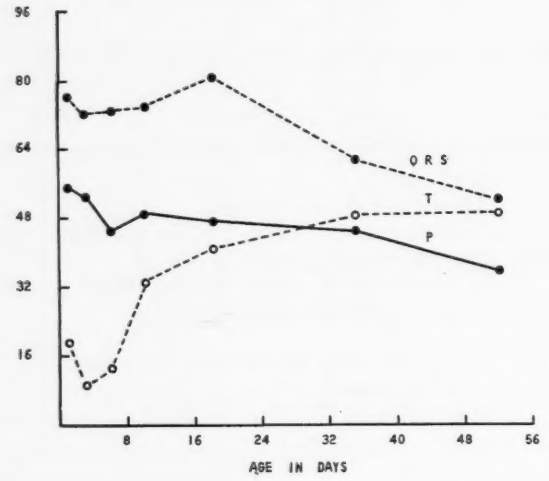


Fig. *1.* Average P-wave, QRS, and T-wave electrical axes, in degrees.

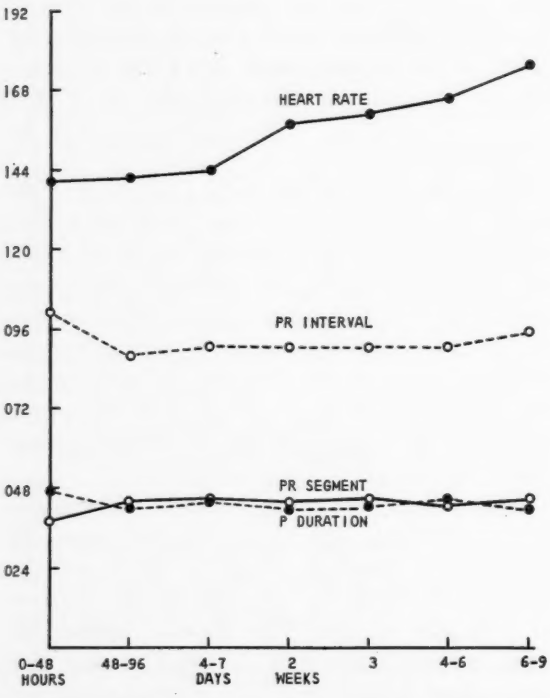


Fig. *2.* Average heart rate, P-R interval, P-R segment, and P-wave duration, according to age

life in the premature infant than in the full-term infant.

The *P-R interval* and *P-R segment* (Fig. 2), which varied but minimally, did not appear to be related to age or heart rate. The *QRS* and *Q-T intervals* (Table II; Fig. 3) seemed to diminish with increasing age and with increased heart rate; however, with the inaccurate method of measurement of the T wave, little significance can be attached to these observations. It was not possible to accurately differentiate U waves in any of these records.

The *electrical axis of the QRS* (Table III) in the premature infant averaged 75 degrees in the first 48 hours of life, with a range of −120 to +135 degrees. This represents a remarkably wider range of values than was seen in the full-term infant. Of interest is the observation that for the individual premature infant there was relatively little variation in the QRS electrical axis in the serial records (Figs. 4 and 5). There was a slight decrease in right axis deviation with increasing age; the average QRS electrical axis changed from 75 degrees at birth to 50 degrees at the age of 9 weeks. This was similarly seen in the full-term infant. Again of interest is the persistence of the wide range of the QRS electrical axis with increasing age in these premature infants (Fig. 6).

The *electrical axis of the T wave* (Table III; Fig. 1) shifted to the right as age increased, with a resultant diminution of the QRS-T angle. Conversely, the T-wave electrical axis in Ziegler's full-term infants tended to shift to the left with increasing age, paralleling the QRS electrical axis. To supplement these observations on

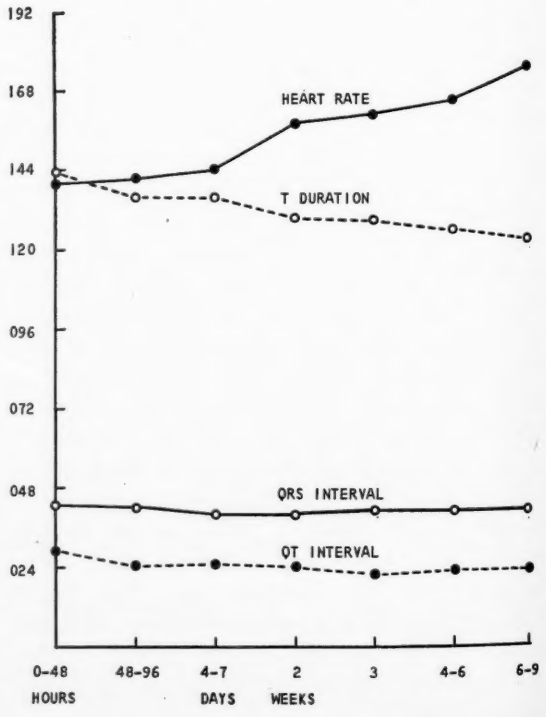


Fig. *3.* Average heart rate, QRS interval, Q-T interval, and T-wave duration, according to age.

Table II. *Average measurements for heart rate, P-R interval, duration of the P wave, P-R segment, QRS interval, Q-T interval, duration of the T wave, and Q-T index at various ages*

Age	*Heart rate*	*P-R interval*	*Duration of P*	*P-R segment*	*QRS interval*	*Q-T interval*	*Duration of T*	*Q-T index*
				*Full-term infant**				
0-24 hr.	125	.099	.051	.048	.065	.294	.143	.421
1 day–1 wk.	138	.095	.0485	.0495	.056	.266	.146	.402
1 wk.–1 mo.	162	.095	.048	.047	.055	.238	.117	.385
1-3 mo.	161	.096	.048	.048	.062	.244	.121	.397
				Premature infant				
0-48 hr.	140	.101	.047	.038	.043	.288	.143	.439
48-96 hr.	142	.088	.042	.044	.042	.251	.136	.308
day 4-7	144	.091	.044	.045	.040	.254	.136	.392
wk. 2	158	.091	.042	.044	.040	.245	.130	.398
wk. 3	161	.091	.043	.045	.041	.220	.129	.362
wk. 4-6	166	.091	.045	.043	.041	.235	.126	.392
wk. 6-9	176	.095	.042	.045	.041	.233	.123	.400

*From R. F. Ziegler: Electrocardiographic Studies in Normal Infants and Children, 1951. Courtesy of Charles C Thomas, Publisher, Springfield, Ill.

Table III. *QRS and T-wave electrical axis (degrees)*

Age	*QRS axis*			*T axis*		
	Average	*Minimum*	*Maximum*	*Average*	*Minimum*	*Maximum*
			*Full-term infant**			
0-24 hr.	137	75	190	77	−10	180
1 day–1 wk.	128	75	190	34	−30	110
1 wk.–1 mo.	105	−5	180	41	−10	130
1-3 mo.	76	35	135	46	0	90
			Premature infant			
0-48 hr.	76	−120	135	19	−60	90
48-96 hr.	72	−115	160	9	−30	45
day 4-7	73	−105	160	13	−60	65
wk. 2	74	−120	160	33	−40	65
wk. 3	80	−120	165	41	10	60
wk. 4-6	62	−130	130	48	25	65
wk. 6-9	52	−95	120	49	30	70
			50 additional premature infants studied			
0-48 hr.	103	−80	155	30	−70	105

*From R. F. Ziegler: Electrocardiographic Studies in Normal Infants and Children, 1951. Courtesy of Charles C Thomas, Publisher, Springfield, Ill.

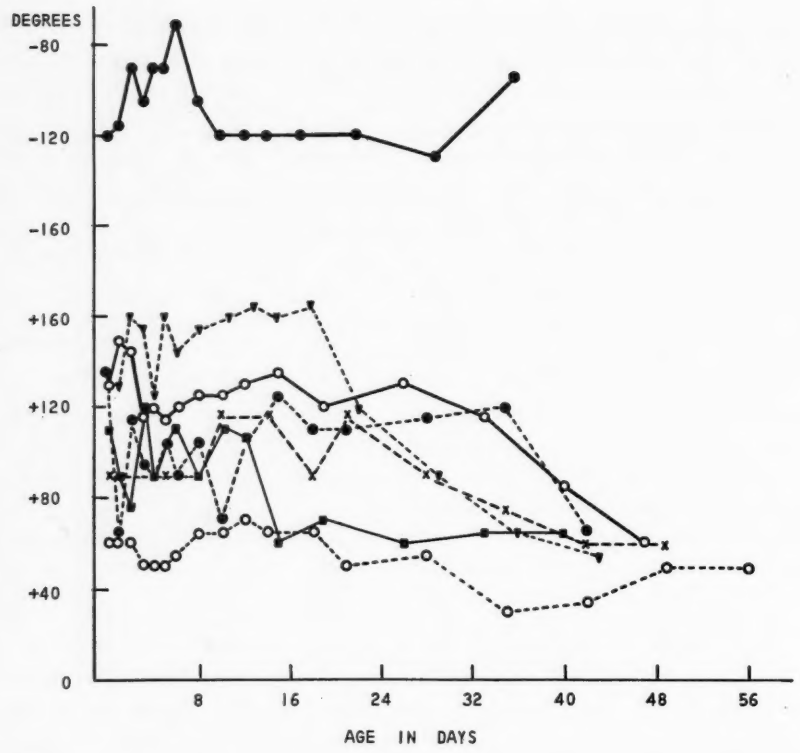


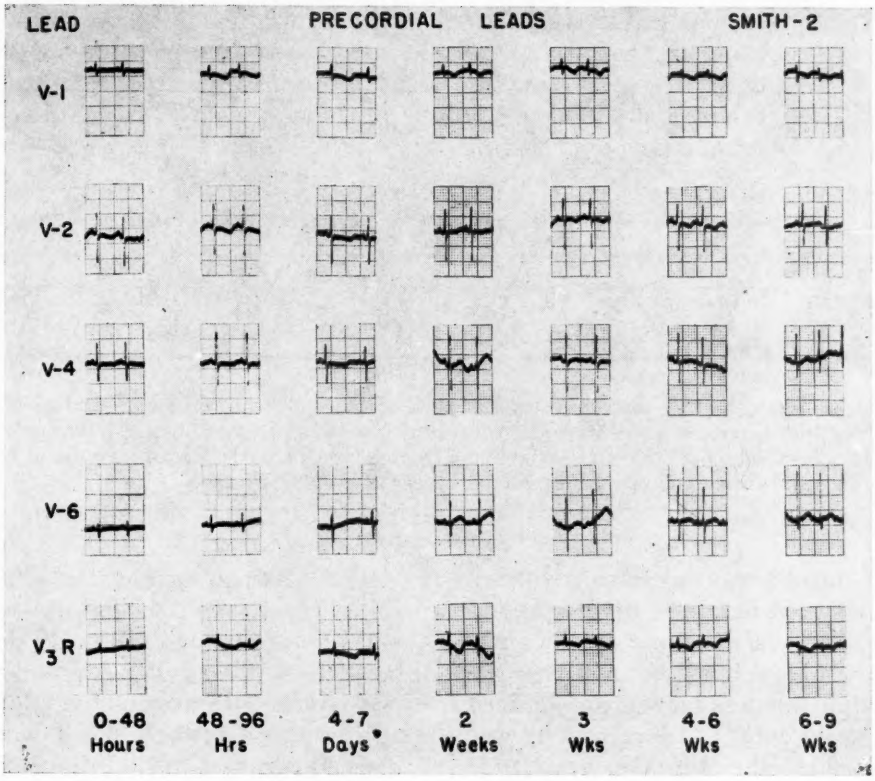
Fig. 4. QRS electrical axis range for each premature infant studied.

the QRS and T vectors, an electrocardiogram was recorded on each of 50 additional premature infants during their first 48 hours of life; analysis of the QRS and T vectors in these 50 premature infants further demonstrated a wider range of values than was seen in the full-term infant (Table III).

The *magnitude of the QRS complex*, as measured by the greatest QRS height in any precordial lead, was unrelated to the age or the body weight of these premature infants.

The greatest *incidence and amplitude of Q waves* (Table IV) was seen in Leads II, III, and aV_F, both in the premature and in the full-term infants. However, the electrocardiogram of the premature infant also showed significant Q waves in Lead aV_L. The Q waves in the electrocardiogram of the premature infant were of significantly lesser amplitude than those in the electrocardiogram of the full-term infant. The absolute incidence of Q waves was less in the premature than in the full-term infant, despite the fact that small Q waves were present in the electrocardiogram of the premature infant in a greater number of leads—i.e., there were fewer Q waves in the electrocardiogram of the premature infant, but they were more widely distributed. No Q waves were recorded in Leads V_{3R}, V_1, or V_2 for the premature infant, nor were Q waves reported by Ziegler in Leads V_1 or V_2 for the full-term infant. There was a striking paucity of precordial Q waves recorded in the premature as compared with the full-term infant. The precordial Q waves, when present in the premature infant, increased in amplitude with lead progression from V_4 to V_6 (as was the case with the full-term infant), and we could demonstrate no significant change in Q-wave amplitude or incidence with increasing age.

The amplitude of the total *RS deflection* (Table V), both in the extremity and in the precordial leads of the electrocardiogram of the premature infant, was considerably less than that reported by Ziegler for the full-term infant. In the limb leads of the electrocardiogram of the premature infant the *R wave* in Leads I and II became taller from birth to 9 weeks of age, whereas R_3 remained relatively unchanged; this has been similarly observed in the full-term infant. The *S wave* in Lead I of the premature infant, unlike that of the full-term



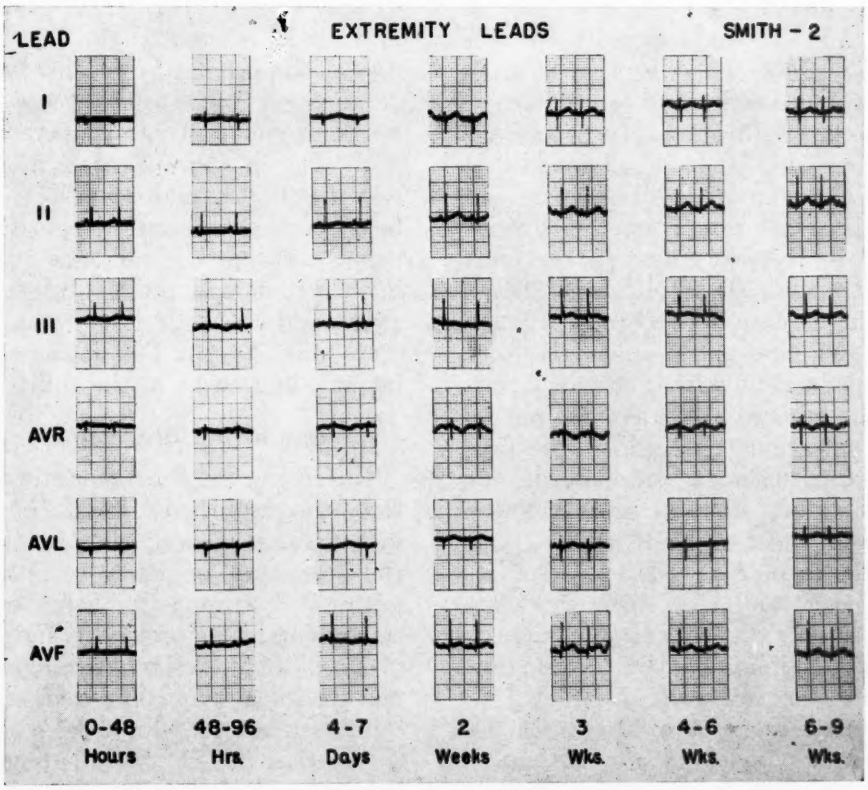


Fig. 5. Selected serial electrocardiograms on one of the premature infants studied (birth weight—1,160 grams).

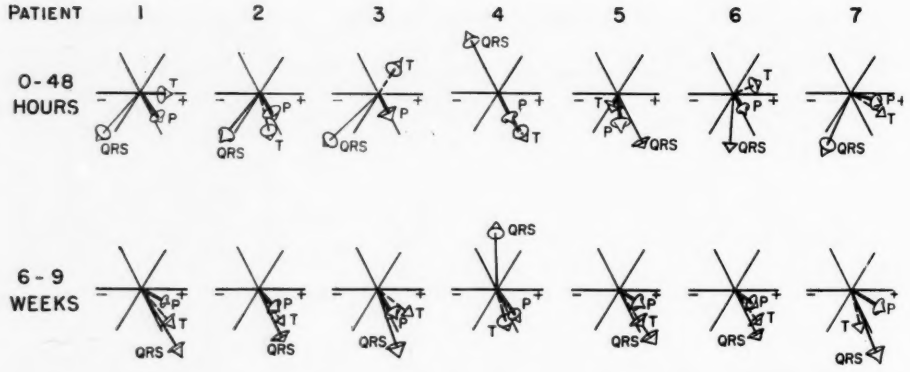


Fig. *6*. Mean P, QRS, and T vectors for each of the 7 premature infants studied. The upper line diagrams the initial electrocardiograms of the series obtained during the first several hours of life. The lower line diagrams the final electrocardiograms of the series, taken when the infants attained a weight of 2,000 grams.

infant, did not change significantly with age; the S wave in Lead III of the premature infant, however, became significantly smaller with advancing age, and this decrease in amplitude was far less pronounced in the full-term infant. In regard to the precordial leads, the R-wave amplitude was greatest in the mid-precordial leads at all ages, both in the premature and the full-term infant. In our records, the R wave in Lead V_6 was markedly greater than the R wave in Lead V_1 (opposite to the observations in the full-term infant), with R_{V6} becoming increasingly prominent with age. The amplitude of all precordial R waves of the premature infant increased with maturity, with the change being least pronounced in R_{V1}; in contrast, the electrocardiogram of the full-term infant showed little increase in precordial R-wave amplitude with age, and R_{V1} and R_{V2} decreased considerably with maturity. Surprisingly, the precordial S wave showed no significant variation with age in the premature infant, whereas the records for the full-term infant demonstrated changes reciprocal with those of the R wave.

The incidence of *RST-segment* displacement (Tables VI and VII), both elevation and depression, was exceedingly pronounced in the premature infant as compared with the full-term infant. This displacement averaged .1 to .2 mm. in the premature infant, both in the extremity and the precordial leads—a far greater amplitude than that seen for the full-term infant.

The *electrical axis of the T wave* (Table III; Fig. 1) shifted slightly to the right with increasing age (19 to 49 degrees from birth to 9 weeks of age), tending to approach the QRS axis, as the QRS concomitantly shifted toward the T-wave axis. In marked contrast to the frequently inverted T_1 and T_{AVL} of the full-term infant, the T_1 and T_{AVL} of the premature infants were usually upright in the first 24 hours of life and tended to remain so. In addition, the T_{V1} of the premature infants was negative or diphasic until week 4 to 6, when it became constantly upright, contrasting with T_{V1} in the full-term infants, which was usually upright at birth and then became predominantly negative. T_{V6} was usually upright at all ages studied, both in the premature and the full-term infants. Precordial T negativity was commonly seen from T_{V2} to T_{V4} in these premature infants, as well as in the full-term infants.

Review of the literature

Interest in the characteristics of the electrocardiographic record of the premature infant was evidenced by sporadic reports in the literature as early as 1913.[2,3] Most authors[4-19] emphasized the evidence of right ventricular preponderance which was observed in the electrocardiograms of premature infants as compared with the records from adults, but varied widely in their delineation of the typical deflections and intervals of the premature-infant record. Although minor differences were described between the electrocardiograms of the

premature and those of the full-term infants, it was generally agreed that there were no characteristics to specifically identify a record as that of a premature infant[4-14,20,21]; however, Thaon[19,22] and Angeli[15] believed that they could identify a specific premature pattern. No relationship was noted between the birth weight of the premature infant and the electrocardiographic pattern.[6,9-11,19]

Table IV. *Per cent incidence of Q waves at various ages*

Age	*I*	*II*	*III*	V_R	V_L	V_F	V_1	V_2	V_3	V_4	V_5	V_6
						*Full-term infant**						
0-24 hr.	3.14	75.0	100.0	72.0	6.28	87.5	0	0	0	7.4	60.0	73.5
1 day–1 wk.	21.5	93.0	96.5	32.0	10.7	93.0	2 cases	0	3.5	25.0	77.2	86.4
1 wk.–1 mo.	22.5	87.5	93.0	55.0	5.0	87.5	0	0	9.1	41.6	87.5	93.0
1-3 mo.	34.2	92.0	95.0	45.0	7.9	89.5	0	0	13.3	50.0	75.0	92.5
						Premature infant						
	I	*II*	*III*	V_R	V_L	V_F	V_1	V_2	V_3	V_4	V_6	V_{3R}
0-48 hr.	0	22.2	33.3	88.9	44.4	33.3	0	0	—	11.1	11.1	0
48-96 hr.	14.3	28.6	28.6	78.6	42.9	28.6	0	0	—	0	21.4	0
day 4-7	9.5	33.3	33.3	76.2	42.9	23.8	0	0	—	0	19.1	0
wk. 2	24.0	44.0	72.0	72.0	32.0	52.0	0	0	—	0	40.0	0
wk. 3	13.3	40.0	60.0	80.0	0	26.7	0	0	—	0	13.3	0
wk. 4-6	21.4	42.9	64.3	64.3	35.7	50.0	0	0	—	7.15	42.9	0
wk. 6-9	6.6	73.3	80.0	60.0	20.0	73.3	0	0	—	13.3	53.3	0

*From R. F. Ziegler: Electrocardiographic Studies in Normal Infants and Children, 1951. Courtesy of Charles C Thomas, Publisher Springfield, Ill.

Table V. *RS deflection amplitude in precordial leads (0.1 millivolts)*

Age	*Average values in precordial leads*				
	V_1	V_2	V_4	V_6	V_{3R}
			*Full-term infant**		
0-24 hr.	27.0	44.4	42.0	9.0	—
1 day–1 wk.	28.0	43.0	35.0	10.0	—
1 wk.–1 mo.	21.0	37.7	29.8	11.8	—
1-3 mo.	20.0	32.8	34.4	13.7	—
			Premature infant		
0-48 hr.	7.39	17.17	14.94	9.00	4.78
48-96 hr.	5.57	15.39	19.25	12.78	5.25
day 4-7	6.45	17.48	19.00	12.60	5.31
wk. 2	7.52	21.30	21.98	13.16	6.98
wk. 3	9.37	22.07	23.93	14.20	6.73
wk. 4-6	7.50	20.61	20.43	15.54	5.46
wk. 6-9	9.47	20.07	21.03	17.20	7.10

*From R. F. Ziegler: Electrocardiographic Studies in Normal Infants and Children, 1951. Courtesy of Charles C Thomas, Publisher, Springfield, Ill.

Table VI. *Incidence of RST segment deviation in extremity leads*

Age	*Incidence in extremity leads*					
	I	*II*	*III*	aV_R	aV_L	aV_F
			*Full-term infant**			
0-24 hr.	3.13	15.6	25.0	9.4	0	9.4
1 day–1 wk.	14.3	42.8	53.6	25.0	10.7	32.1
1 wk.–1 mo.	20.0	17.5	15.0	0.5	0.25	10.0
1-3 mo.	5.27	5.27	13.2	0	2.64	7.9
			Premature infant			
0-48 hr.	33.3	33.3	88.9	22.0	33.3	66.7
48-96 hr.	50.0	50.0	64.3	50.0	42.9	57.1
day 4-7	42.9	47.6	61.9	71.4	47.6	52.3
wk. 2	84.0	72.0	68.0	52.0	48.0	72.0
wk. 3	66.6	93.3	73.3	60.0	53.3	80.0
wk. 4-6	50.0	78.6	78.6	35.7	42.9	64.3
wk. 6-9	66.6	100.0	53.3	40.0	53.3	60.0

*From R. F. Ziegler: Electrocardiographic Studies in Normal Infants and Children, 1951. Courtesy of Charles C Thomas, Publisher, Springfield, Ill.

Table VII. *Incidence of RST segment deviation in precordial leads*

Age	*Incidence in precordial leads*				
	V_1	V_2	V_4	V_6	V_{3R}
			*Full-term infant**		
0-24 hr.	25.9	51.9	80.0	7.4	—
1 day–1 wk.	50.0	37.5	91.0	12.5	—
1 wk.–1 mo.	41.7	25.0	75.0	8.35	—
1-3 mo.	23.1	3.85	75.0	11.55	—
			Premature infant		
0-48 hr.	77.8	88.9	66.7	66.7	55.6
48-96 hr.	78.6	64.3	78.6	71.4	42.9
day 4-7	66.7	66.7	80.9	71.4	71.4
wk. 2	88.0	56.0	84.0	60.0	96.0
wk. 3	86.7	46.7	60.0	86.7	93.3
wk. 4-6	64.3	57.1	78.6	42.9	71.4
wk. 6-9	93.3	33.3	26.7	66.6	86.7

*From R. F. Ziegler: Electrocardiographic Studies in Normal Infants and Children, 1951. Courtesy of Charles C Thomas, Publisher, Springfield, Ill.

Wide variation in the electrical axis of the QRS complex and disturbances in impulse mechanism and in conduction were attributed to cardiovascular immaturity, since they were seen without associated clinical heart disease.[3,8,9,18,21] An increased

incidence of electrocardiographic abnormalities was reported in the younger premature infants in the first days of life.[10,11,17]

Regular sinus rhythm was usually present in the premature infant, with a considerably lesser incidence of arrhythmias reported than in the full-term baby[6,7,10,12,14,18,19,22]; Angeli,[15] on the other hand, reported sinus arrhythmia to be characteristic, and Nadrai[23] noted frequent extrasystoles. The electrocardiogram of the premature infant was usually described as having lower voltage than that of the full-term infant, this being most prominently seen in the QRS complex; Engel's work[20] did not confirm this. Seham[24] reported the voltage of the electrocardiogram of the premature infant to be too low to obtain satisfactory records for analysis. A decrease in the duration of all electrocardiographic deflections in the record of the premature infant was reported by Angeli,[15] Stoermer,[12] Thaon,[22] and Nadrai[11]; this was variously attributed to increased heart rate, smaller cardiac muscle mass, and cardiovascular immaturity.

Gomirato-Sandrucci and Crosato[6] observed no difference between the P wave of the premature infants and that of the full-term infants, whereas most other observers emphasized the prominent P waves (usually described as P pulmonale) in the records of premature infants.[7,9,10,19,22,23] Mader and Lanza[10] and Stoermer's[12] measurements of the Q-T interval of the premature infant were within normal limits; a prolonged Q-T interval was more frequently commented upon.[11,14,15,19,22,25] Deviation of the S-T segment from the isoelectric line, associated with low voltage or abnormally directed T waves, was commonly described.[5,10-13,15,19,22,25]

Much of the disparity noted above may be accounted for by the lack of uniformity in the electrocardiographic equipment used, the small numbers of cases in most series, the differences in the criteria for prematurity, and the variations in the age of the premature infant at the time of the electrocardiographic recording.

Discussion

We have, without particular difficulty, obtained satisfactory serial electrocardiographic records on 7 premature infants. Analysis of these tracings shows some similarity to the characteristic electrocardiographic features in the records of full-term infants: right axis deviation of the QRS and frequent T-wave inversion in the right and mid-precordial leads. However, distinct differences are equally apparent.

Although we are unable to offer logical and satisfactory explanations for these differences, it seems of value to state a few possibilities which come to mind. The P wave of the electrocardiogram of the premature infant was noted to be of significantly greater amplitude than that of the full-term infant; the greater pulmonary arterial pressure from the immature pulmonary vascular bed and the increased mechanical resistance due to incomplete expansion of the lungs may well be the responsible factors.

The generally smaller QRS deflection seen in all electrocardiographic leads in the premature infant may be explained by the relatively smaller cardiac mass available to generate electrical activity.

Quite obviously, any change in cardiac configuration can influence the spatial vector pattern reflected in the electrocardiogram. The wider range of values for the electrical axis of the QRS complex, and the fewer and smaller Q waves observed in the premature infant may in some way be related to the globular cardiac configuration so often seen in the premature baby.

RST-segment deviation from the isoelectric line is much more pronounced in the premature infant. The question is raised whether this repolarization abnormality is due to the somewhat more rapid heart rate of the premature infant or to actual myocardial anoxia resulting from an immature respiratory system.

The T waves of the premature infant, particularly in Leads I, aV_L, and V_1, were opposite in direction to those observed in the full-term infant. This again is explicable either as a secondary T-wave change (the QRS differing in the premature and the full-term infants), or as a primary repolarization abnormality related to pulmonary vascular immaturity and hypoxia. An alternate or additional factor both in the RST-segment and T-wave changes is the somewhat abnormal electrolyte pattern

of the premature infant, probably secondary to the immaturity of renal function.

Conclusion

In a preliminary study of the characteristics of the electrocardiogram of the normal premature infant, several differences from the electrocardiogram of the full-term infant are apparent. The electrocardiogram of the normal premature infant is seen to have: (1) greater P-wave amplitude, (2) wider range of the QRS electrical axis, (3) smaller QRS amplitude, (4) fewer and smaller Q waves, and (5) greater S-T—segment deviation.

Complete statistical analysis of our data has not been submitted because the number of individuals studied was relatively small and these data would therefore have limited significance. However, the authors have more detailed numerical values for the several components of the electrocardiogram of the premature infant.

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The loud musical diastolic murmur of an abnormal rheumatic chorda

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McKusick[1] in his excellent monograph on cardiovascular sound has defined musical murmurs as murmurs presenting a quality "best defined by the proved ability to represent the murmur by conventional musical notation." In the spectrogram, musical features are characterized by the presence of harmonics—the most objective definition of musicality[1]; and in the conventional phonocardiogram, musical murmurs are often recognized by their rapid high-frequency vibrations.

Musical murmurs usually occur in systole, and originate from the aortic valve, the mitral valve, or extracardiac sources. Musical diastolic murmurs, on the other hand, seldom occur except in valvular deformities. The mitral valve has very rarely been implicated. McKusick[1] described one patient cured of subacute bacterial endocarditis who had an unusual systolic and diastolic apical murmur, and another who had a musical presystolic murmur. Calo[2] reported a musical apical presystolic murmur in a patient who had syphilitic aortitis with aortic incompetence.

In this report we describe a patient who had a striking musical diastolic and presystolic murmur superimposed on the conventional murmurs of mitral stenosis. The murmur sounded like the vibration of a musical string instrument. It was unaffected by mitral valvular operation and was attributed to an abnormal, thickened rheumatic chorda tendinea strung across the orifice of the mitral valve.

Case history

V. L., a 28-year-old Coloured male, was first seen in February, 1957, complaining of progressive effort dyspnea which had been present for 1 year. He had been compelled by his symptoms to change his occupation from bricklayer to petrol attendant but was not sufficiently disabled to warrant an operation.

On examination there was no evidence of heart failure, the jugular venous pressure was normal, the pulse felt small, and the blood pressure was 130/80 mm. Hg. The apex was normal in situation and quality. There was a long diastolic rumble with presystolic accentuation and a Grade 2/6, long mitral systolic murmur. The opening snap was barely audible, and the first sound was not accentuated, suggesting calcification of the mitral valve. The latter condition was confirmed on screening. An ejection sound was present at the base and fourth left intercostal space, with a high-pitched "cooing dove" aortic early diastolic murmur of no apparent hemodynamic significance. The electrocardiogram showed marked left atrial hypertrophy, and on x-ray examination the left atrium and pulmonary arteries were observed to be moderately enlarged and the left ventricle full sized. Operation was postponed.

Within 7 months his condition had deteriorated considerably; cough, hemoptysis, and orthopnea developed and required digitalization. From then

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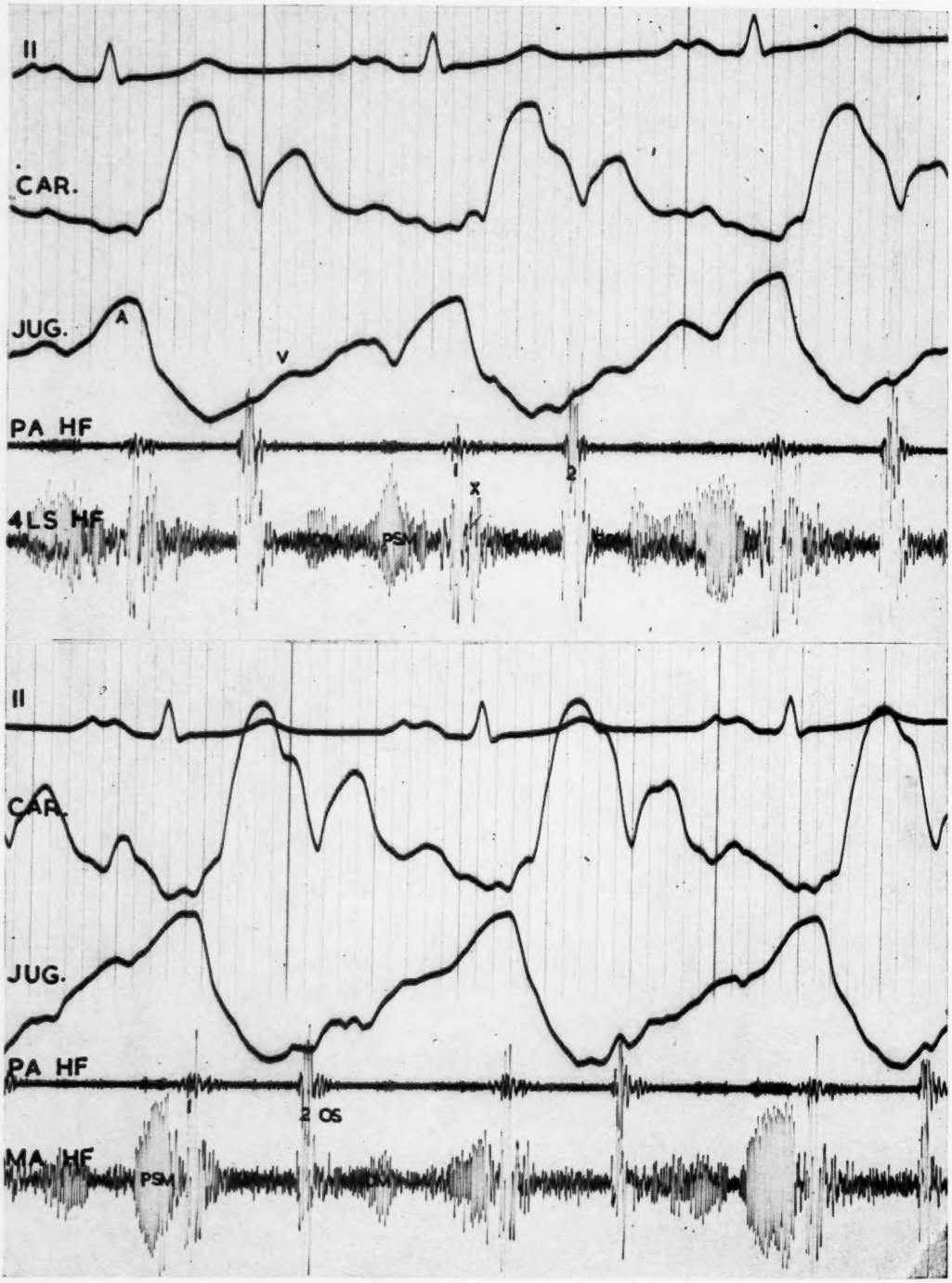

Fig. *1.* High-frequency phonocardiograms taken at the pulmonary area (*PA*), fourth left intercostal space (*4LS*), and mitral area (*MA*), with synchronous carotid artery (*CAR*) and jugular venous tracings (*JUG*). At the mitral area the high-pitched musical murmur is well shown. The vibrations are very rapid but evenly spaced, and, although they vary in intensity from cycle to cycle, presystolic accentuation is always present. The murmur radiates to the fourth left intercostal space and pulmonary areas, where it has been recorded. The presystolic murmur ceases before the slightly delayed first heart sound, and the P-R interval is full. Mid-diastolic vibrations are also present. A pansystolic murmur and opening snap are also shown. The high-frequency musical murmur is superimposed on the usual low-frequency diastolic murmur of mitral stenosis. At the fourth left intercostal space, in addition to the musical murmur, an early diastolic murmur of aortic incompetence has been recorded. A pulmonary ejection click (*X*) and a pansystolic murmur are also present. At the pulmonary area the sounds and murmurs have been attenuated. Splitting of the second sound is present as well as an opening snap. The pulmonary ejection click and musical diastolic murmur are also recorded.

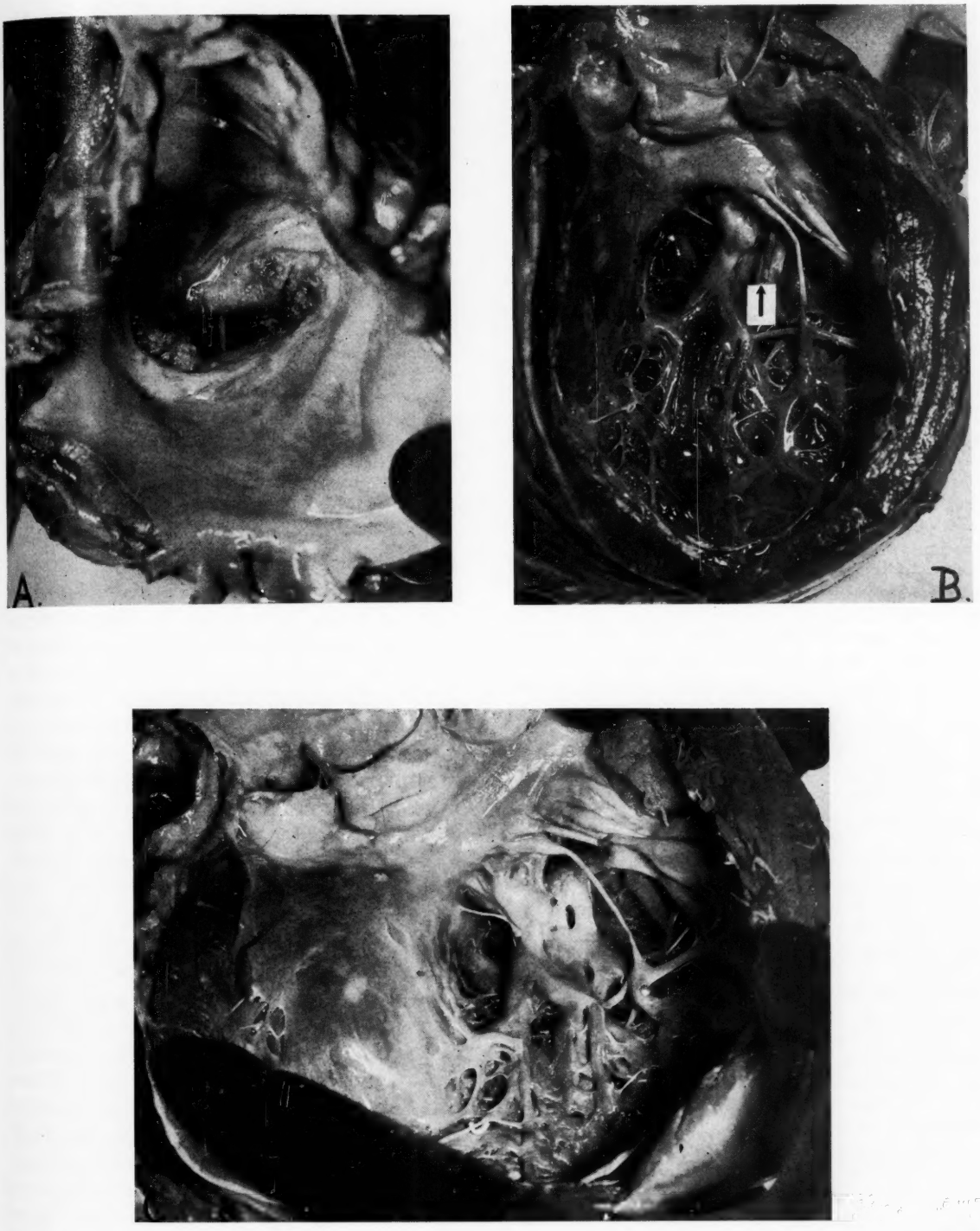

Fig. 2. Appearance of the mitral valves, left atrium, and left ventricle at necropsy. *A*, Viewed from the left atrial cavity. The stenosed incompetent mitral valves are well shown, with fusion of the commissures and calcification of the cusps. The abnormal thickened chorda is stretched across the orifice of the valve. *B*, Viewed from the left ventricular cavity. The probe (*arrow*) has been passed through the orifice of the mitral valve into the left ventricle. The hypertrophied and dilated left ventricle is shown with an abnormal papillary muscle from which the thickened abnormal chorda runs to the mitral valve leaflet. The diseased mitral and aortic valves are also visible. *C*, The atypical chorda has been put on the stretch by slightly displacing the papillary muscle with a pin. The abnormal position of this thickened chorda results in it being in the direct line of the flow of blood from left atrium to left ventricle. The normally situated chordae and papillary muscles show the typical rheumatic thickening, shortening, and cross-fusion. The thickening and slight fusion of the aortic valve cusps is also shown.

on, until he underwent an operation 3 months later, the auscultatory findings were confusing and difficult to interpret. The "cooing dove" murmur altered in timing and quality, varying considerably in intensity from cycle to cycle (Fig. 1) and also in position in diastole. To the ear, there were three distinct diastolic murmurs (not readily differentiated on the phonocardiogram)—an early diastolic murmur of aortic incompetence, a mid-diastolic murmur of mitral stenosis, and a high-frequency "violin string twang" superimposed on the latter but varying in intensity and situation. It was always loudest in presystole (Fig. 1), stopping before the first sound, but was also superimposed on the mitral mid-diastolic murmur. In addition, systolic murmurs were present at the mitral and tricuspid areas, suggesting mitral and tricuspid incompetence.

Operation was advised in view of the progressive nature of the symptoms and the signs which suggested dominant stenosis, although some degree of incompetence was anticipated. At operation the valve was slit-like, measured 1.3 square centimeters,[3] and was encrusted with calcium, particularly toward the posteromedial commissure. A distinct regurgitant jet was present, but there was no gross reflux and the valves were regarded as being moderately fibrosed. The anteromedial cusp ballooned out well, and digital splitting was achieved by the padded finger; a valve orifice of over 5 square centimeters was obtained, associated with only slight increase in the regurgitant jet. Left atrial pressure fell from 25/18 to 18/11 mm. Hg, with little change in pulse form. Histologic examination of the left atrial biopsy specimen showed a number of active Aschoff nodes, suggesting recent inflammation. In the lung biopsy specimen the pulmonary arteries were thick walled, and a vessel partially occluded by organized thrombus was found.

The immediate response to the operation was satisfactory. Three months later he had improved considerably despite the persistence of postoperative atrial fibrillation. On auscultation the variable high-pitched, twanging diastolic murmur was superimposed on the aortic and mitral diastolic murmurs, but the presystolic murmur had disappeared. The mitral systolic murmur had increased in intensity.

The unusual auscultatory findings were attributed to an atypical thickened chorda which straddled the orifice of the mitral valve, and which vibrated during the flow of blood from the left atrium to the left ventricle.

Digitalization was followed by several attempts at correction of the arrhythmia with quinidine, without success. The drug was abandoned after the development of a rapid regular tachycardia due to 1:1 rhythm with aberration.

Thereafter the condition of the patient deteriorated rapidly, and within a month he was readmitted for control of severe congestive cardiac failure, with a jugular venous pressure of over 25 cm., a four-finger, tender, pulsating hepatomegaly, ascites and signs of mitral stenosis, aortic incompetence, and mitral and tricuspid incompetence. After an initial response to treatment he became refractory to diuretics, developed gross intractable heart failure, and died 17 months after operation.

Necropsy revealed gross congestion of all organs, with subcutaneous edema, ascites, pleural effusion, pulmonary edema, and cardiac cirrhosis. The heart weighed 705 grams; both atria were hypertrophied and dilated. The left ventricle was dilated and probably hypertrophied, and the right ventricle was markedly hypertrophied and dilated, with severe atheroma of the pulmonary tree.

The mitral orifice was an oval, narrow, stenosed cleft which admitted the tip of one finger, and had rigid calcified cusps. The site of the previous operative splitting could not be determined. From the atrial aspect (Fig. 2*A*) a thickened abnormal chorda tendinea could be seen stretched across the mitral orifice. From the ventricular aspect the chordae were considerably thickened and shortened, and the abnormal chorda (Fig. 2*B*) could be seen stretched across the inflow tract of the dilated left ventricle. The aortic cusps (Fig. 2*C*) were slightly thickened and there was fusion of the commissures between two of the cusps, without significant stenosis or incompetence, however.

Discussion

We have reported on a patient in whom musical mid-diastolic and presystolic murmurs were heard and recorded phonocardiographically during life; the murmurs were associated with an unusual malformation of a chorda tendinea found at necropsy. The patient developed all the signs and symptoms of severe obstructive mitral valvular disease, with trivial incompetence. On the first examination the musical murmur was mistaken for a "cooing dove" murmur of aortic incompetence. Re-examination, however, revealed a distinctive murmur occurring in mid-diastole and presystole. The cadence was that of a plucked string of a musical instrument, varying from cycle to cycle, both in position and intensity but always diastolic. Although presystolic accentuation was present, the sound was clearly separated from the first heart sound. At mitral valvotomy no pericardial disease was detected and no extracardiac cause for the unusual observations could be found. Severe rheumatic mitral valvular stenosis with slight incompetence was recognized and commissurotomy was performed. After the operation there was no alteration in the character of the musical murmur except for the disappearance of the presystolic accentuation with the development of atrial fibrillation. The improvement after operation was short-lived, and necropsy 17 months later revealed severe chronic congestive cardiac failure with unrelieved mitral stenosis, some mitral incompetence, and slight involvement of the aortic valve.

The murmurs were attributed in life to an abnormal attachment of a chorda tendinea which straddled the orifice of the mitral valve, and this was confirmed at necropsy.

Huchard,[4] in 1893, was the first to describe a musical murmur due to aberrant tendons crossing the stream of blood flow. Because these murmurs appeared only later in life, it was postulated that the aberrant tendons had first to be tautened by ventricular dilatation before being able to cause murmurs. Murmurs produced in this fashion have been likened to the sound produced by the aeolian harp.[5] Huchard's murmur, however, was systolic in time. Continuous musical murmurs have been attributed to tensing of an abnormally developed Chiari network.[6,7] Diastolic murmurs of mitral origin are even rarer; most diastolic murmurs are either aortic or extracardiac in origin.

In our case it is postulated that a congenitally abnormal chorda was thickened, shortened, and tautened by the rheumatic process. This resulted in a shortened chorda strung across the abnormal stenosed orifice of the mitral valve. During the flow of blood from the left atrium to the left ventricle the chorda, tautened by the dilating ventricle, was thrown into vibration and produced a sound like the plucking of a harp string. An increased flow of blood during contraction of the hypertrophied left atrium produced accentuation of the murmur. The variability of the murmur is presumably attributable to change in position of the chorda from cycle to cycle, and possibly also to the change in the degree of its tautening by the dilating ventricle during diastole. The absence of a murmur during systole can be explained by the postulate that the regurgitant stream of blood from the left ventricle was directed away from the chorda. Straddling the mitral orifice as it did, the chorda could hardly fail to be involved during forward flow from left atrium to left ventricle.

Summary

A case of rheumatic heart disease with dominant mitral stenosis is presented in which a peculiar musical mid-diastolic and presystolic murmur was heard and recorded phonocardiographically.

The murmur was characterized by the peculiar tonal qualities simulating the vibrations produced by a stringed instrument, such as a harp. The murmur varied in intensity from cycle to cycle and also in position, and was maximal in presystole. At necropsy, an abnormal anatomic chorda tendinea, pathologically thickened by rheumatism, was found to be strung across the mitral orifice.

The musical sounds in diastole were attributed to vibration of the abnormal chorda during the flow of blood from the left atrium to the left ventricle.

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Parasystole with a rapid ventricular center

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Parasystole is of special interest among the disturbances of ectopic impulse formation. First, a parasystolic arrhythmia is of clinical importance because the ventricular form usually indicates the presence of organic heart disease. Second, parasystole, although not rare, is frequently overlooked because it is not differentiated from extrasystole. Third, the mechanism of parasystole needs to be explained more satisfactorily. In this paper we have collected examples of parasystole from 8 patients which contribute to the better understanding of its mechanism.

An important feature of parasystole is the phenomenon that the parasystolic center from which ectopic impulses arise is not influenced by the spread of normal impulses over the heart. This requires an explanation, since according to a principle of cardiac physiology, all fibers of the heart are depolarized by the spread of an excitation. It has been assumed that the center is protected by a "block" zone.[9] The "block" prevents an outside stimulus from disturbing the parasystolic center. This hypothesis was accepted only after certain experimental studies established two facts. One, parasystole could be induced in the dog heart, and the parasystolic center was not disturbed by the basic rhythm.[10] Two, the production of a "unidirectional block" which permitted impulses to be transmitted in a strip of muscle in only one direction demonstrated that impulses formed in a center may activate the heart while the center remains unaffected by the normal rhythm.[1,14] Unidirectional block, however, which is seen only under very special conditions, would be difficult to postulate during the prolonged periods over which parasystole has been observed in some patients.

Although the concept of a protected ectopic parasystolic center is fundamental to explain parasystole, the term "block" was said to be inappropriate because there is no evidence of a disturbance in conduction usually implied by this word. Instead, the term "protection" of the parasystolic center has been proposed.[2] This protection was ascribed to the high rate of formation of impulses in the center.[10] Experiments on the dog heart made hypodynamic by quinine have shown rates of impulse formation up to 300 per minute in a center induced by mechanical or electrical stimulation, with only every second impulse propagated. In these experiments a 2:1 exit block usually existed. Because of the rapid formation of stimuli, the center was refractory to outside impulses.

Later studies sought to explain protection by a decreased excitability of the center or by infra-threshold impulses.[4] According to this view a parasystolic arrhythmia would depend only on the relation between the strength of the impulse and the excitability of the center. This explanation is not entirely satisfactory because it fails to

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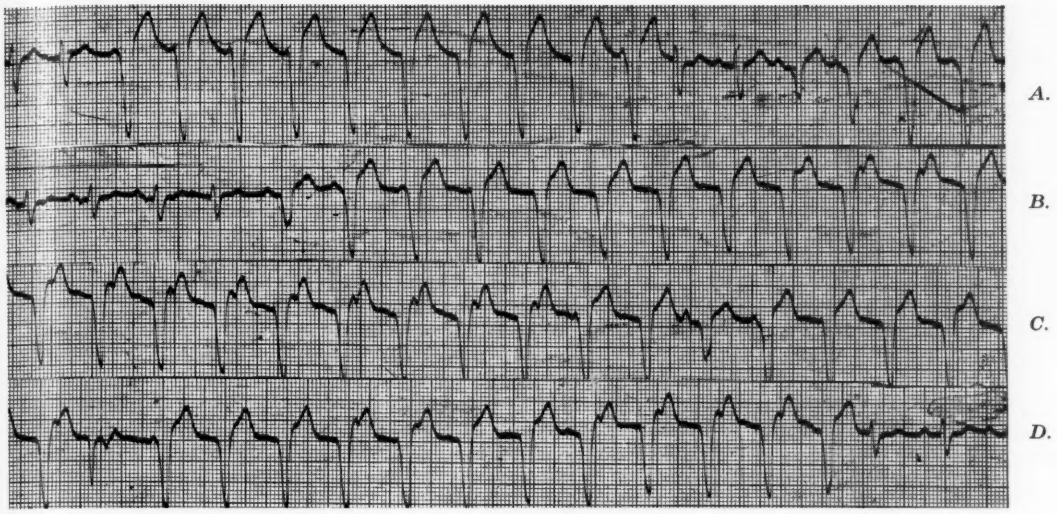

Fig. *1.* Observation 1. The tracings were taken in Lead II. They show a ventricular tachycardia which is interrupted in *A* by sinus beats; measurements show that these sinus beats do not disturb the activity of the ectopic center. In *C* and *D* the sinus rhythm sometimes overtakes the tachycardia after the manner of a dissociation with interference.

indicate why a conducted impulse would not completely depolarize a parasystolic center, especially one in which slow diastolic depolarization, a characteristic feature of impulse formation, had already begun to depolarize the cell membrane. On the basis of our present knowledge, supported by the present study, we believe that the most logical explanation for protection remains our original one, viz., rapid formation of impulses in the parasystolic center.

Observations

Observation 1. This 50-year-old man with diabetes, coronary sclerosis, and congestive heart failure while on a maintenance dose of 0.1 Gm. of digitalis daily, developed a rapid parasystolic center protected from the sinus beats. Fig. 1,*A* (Lead II) shows a ventricular tachycardia with a rate of 110 beats per minute. The individual ectopic beats are not conducted in reverse manner back to the atria. Successive ectopic periods measure 52, 56, 55, 56, 56, 54, 54, 56, 54.* Sinus rhythm soon overtakes the ectopic rhythm, with two sinus beats which are followed by a combination beat and the reappearance of ectopic beats. The interval between the two ectopic beats separated by the sinus beats measures 222, or exactly four ectopic periods of 55.5 each.

*These figures indicate hundredths of a second.

The same pattern reappears in *B*, *C*, and *D* of Fig. 1, taken several days later. In both *C* and *D* a sinus beat activates at least a portion of the ventricles. In both instances the interval between the two ectopic beats next to the summation beat equals two ectopic periods.

Observation 2. This 67-year-old man who had an inferior wall infarction, as indicated in the standard leads in Fig. 2,*A*, developed a rapid ventricular center protected from the sinus rhythm as in parasystole. This ventricular tachycardia with a rate of 115 per minute was registered in Leads II and III (*B* and *C* of Fig. 2) 6 days after the infarction. As in the first observation, the ventricular ectopic beats were not conducted back to the atria, and sinus beats occasionally reached the ventricles (Fig. 2,*D* and *E*). Successive ectopic intervals measure between 52 and 55. When separated by sinus or combination beats the interval doubles, becoming 104, 107, 105, 108, 104, and 106, that is, two ectopic intervals. It is obvious, therefore, that the ectopic center is protected from the sinus beats, and that we are dealing with a parasystole with a rapid center.

Observation 3. This 88-year-old man with coronary sclerosis and atrial fibrillation controlled by 0.2 Gm. of digitalis daily demonstrated both a ventricular parasystole and exit block. All tracings were

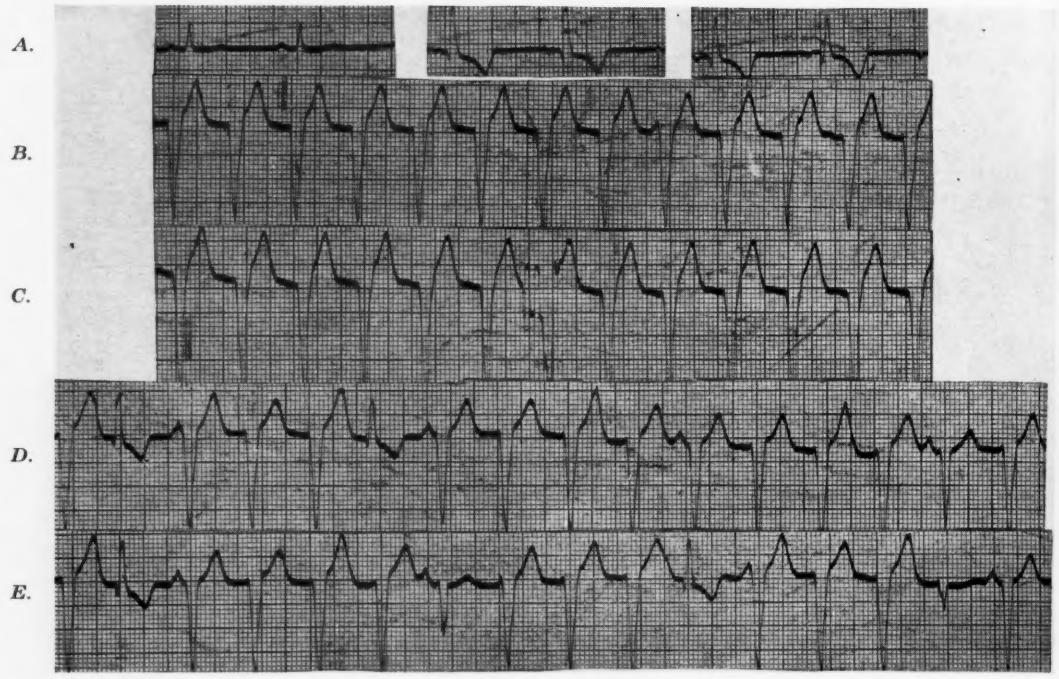

Fig. 2. Observation 2. *A* shows evidence of an inferior wall infarction in the three standard leads. A ventricular tachycardia appeared (*B*) with a rate of 115. Here again, as in Observation 1, sinus beats occasionally succeed in reaching the ventricles (*C* and *D*); they do not disturb the activity of the ectopic center.

registered in Lead II. In Fig. 3,*A* a ventricular tachycardia follows two beats conducted from the atria. The interectopic periods of the tachycardia which vary between 62 and 73 signify rates between 96 and 82 beats per minute. The successive ectopic periods measure 73, 69, 67, 65, 64, 63, 62, 62, and 62. The rate of the ectopic center during the uninterrupted ectopic rhythm gradually increases. This phenomenon is not a rare observation in parasystole and has been described repeatedly. In Fig. 3,*B* the tachycardia ends, and groups of bigeminy without fixed coupling appear. Ectopic intervals measure 60, 61, 62, and 60. After the tachycardia the ectopic distances measure 187, 182, and 187 (3 × 62 or 60.5). The last ectopic beat is not shown.

In Fig. 3,*C*, a long pause occurs, measuring 263 (or 4 × 66), which contains an extrasystole and a conducted beat. Interectopic periods between 64 and 68 then follow.

In the subsequent tracings of Fig. 3 (*D* to *G*) the pauses which contain conducted beats are always a multiple of the basic ectopic interval. During these pauses an exit block must exist, since ectopic impulses fail to activate the ventricles, even if such impulses appear outside of the refractory phase.

The tracings in Fig. 4 were obtained from this patient on the same day. In *A*, taken in Lead I, the first impulses after a long interval without ectopic beats appear at a slow rate, with periods of 72, 70. The rate rapidly increases, with successive periods shortening to 68, 66, and 64. Tracings *B* through *E* demonstrate an exit block. In *E* a beat representing the summation of an ectopic beat and a conducted beat is followed by ectopic intervals of 66, 62, 62, 62, and 38. The sudden halving of the interval suggests that the ectopic center actually works at a rate of about 158 and that most of the ectopic intervals result from a 2:1 exit block.

Observation 4. The presence of exit block is also suggested in the tracings (Fig. 5) obtained from a 48-year-old nondigitalized, hypertensive man admitted with an acute hemiplegia. In addition to sinus rhythm, extrasystoles, and late ectopic beats the electrocardiogram shows a marked intraventricular block. In Fig. 5,*D* the presence of ectopic intervals of 84 and 42 suggest a

center working at a rate of 140 halved by a 2:1 exit block to 70. In the beginning of *D*, recorded in Lead V_2, three ectopic beats, the last deformed by a summation with a sinus beat, present a rate of 70 with interectopic intervals of 84. After two sinus beats—the first is slightly deformed by summation—two ectopic beats occur, separated by an interval of 42, which represents a rate of 140. Likewise, the interval of 215 (5×43) between the third beat in *D* and the next ectopic beat suggests an ectopic rate of about 140, partially suppressed by an exit block. Tracing *E* of Fig. 5 shows an

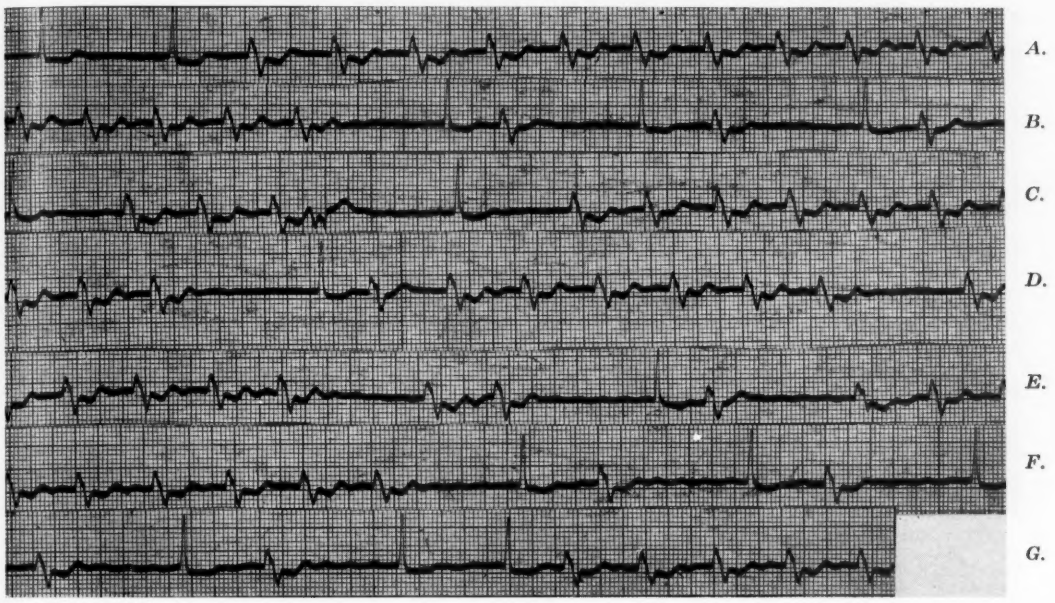

Fig. *3*. Observation 3. All tracings were taken in Lead II. There is atrial fibrillation (*A*), and the patient was under digitalis therapy. The tracings show a rapid ventricular ectopic rhythm, and the intervals without ectopic beats are a multiple of the ectopic interval. There is a 2:1 exit block in several tracings.

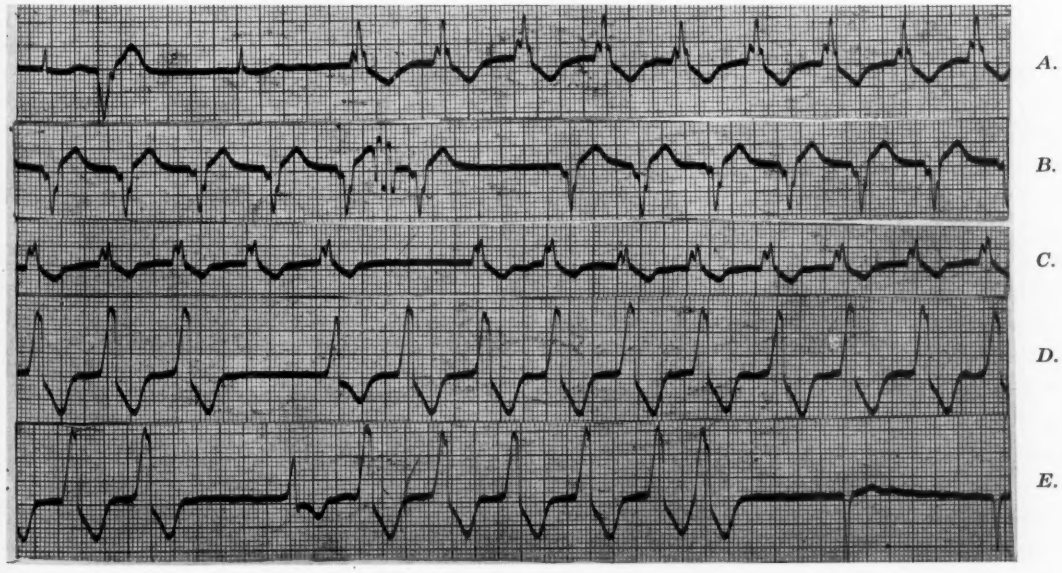

Fig. *4*. Observation 3. The tracings were taken in Leads I, aV_L, and aV_F; tracings *D* and *E*, which are continuous, were recorded in Lead V_1. The tracings show exit block with parasystole, and a sudden premature ectopic beat in *E*.

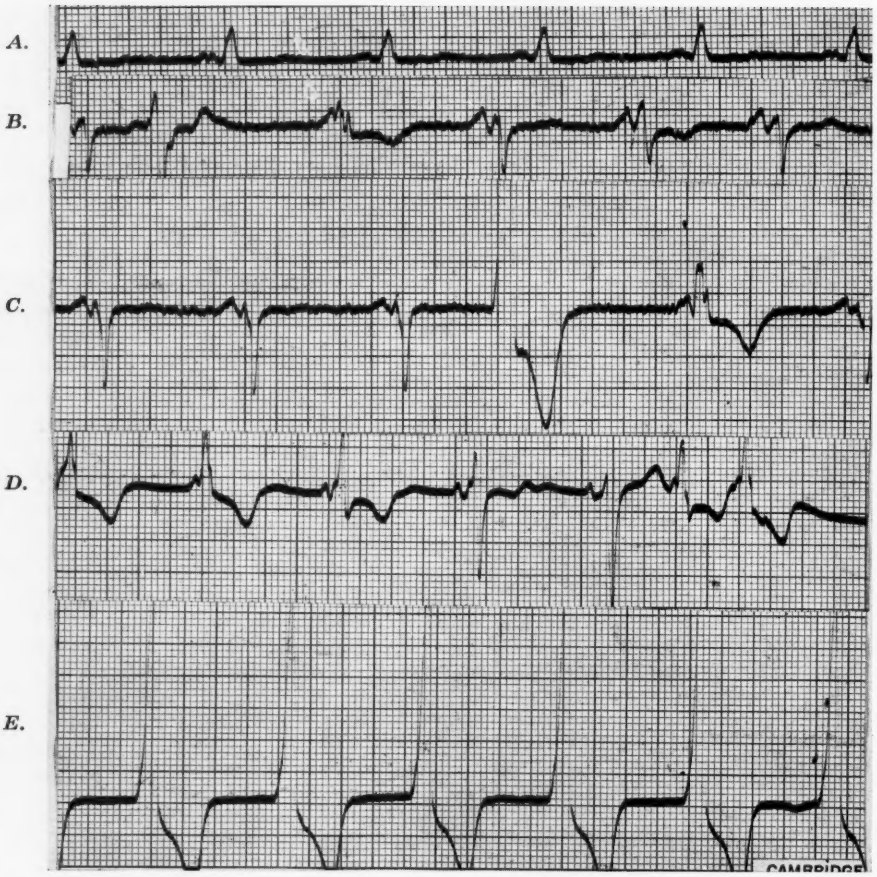

Fig. 5. Observation 4. The standard leads show an intraventricular block and premature ectopic beats. In *D* (Lead V_2), ectopic beats appear. The intervals between the first three are 86 and 84; the interval between the last two is 42. This suggests that a center is active, with an ectopic interval of about 42, and that in the beginning of *D* and in *E* (Lead V_5) a 2:1 exit block prevails.

ectopic rhythm with an interval of 84, corresponding to a rate of 70, which could easily represent a 2:1 block.

Unfortunately, no further tracings were obtained from this patient. The arrhythmic pattern indicates a parasystolic center with a rapid rate of 140 subjected to an exit block which reduces the ectopic rate to 70.

Observation 5. This 80-year-old man with coronary sclerosis exhibited a parasystole with an ectopic rate of about 80 which, on carotid pressure, not only slowed but at times exhibited extrasystoles coupled to the automatic beats.

In tracing *A* of Fig. 6, combination and normal sinus beats are sandwiched between ectopic ventricular tachycardias. Although the patient did not receive digitalis, the P-R is prolonged to 0.24. The ectopic intervals of 78, 74, and 73 represent a heart rate between 77 and 82. The interval between the fourth and tenth complexes measures 456, or 6 × 76. In tracing *B*, in which only a single sinus beat is seen,

Table I

73—219	(3 × 73)
72—218	(3 × 72.5)
72—218	(3 × 72.5)
73—520	(5 × 74.5)
74—448	(6 × 74)
77—314	(4 × 78)
74—298	(4 × 74)
79—382	(5 × 77)
76—306	(4 × 76)
77—308	(4 × 77)
76—304	(4 × 76)
76—306	(4 × 76)
76—304	(4 × 76)

The first figure represents the ectopic intervals which were directly measured in Observation 5, and then the duration of long intervals filled by sinus beats.

the interval between the ectopic beats adjacent to the sinus beat is 147, or 2 × 73.

In long tracings taken from this patient, ectopic intervals varied between 72 and 79 on different days. Often, several sinus beats replaced the ectopic beats, causing long intervals free of ectopic beats. All of them are seen in Table I, which gives

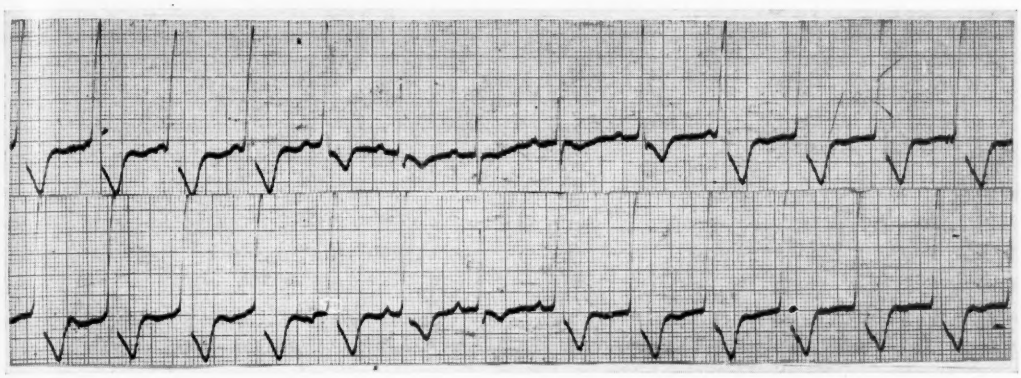

Fig. *6*. Observation 5. Both tracings show an ectopic rapid rhythm interrupted by sinus beats. The long interval without ectopic beats which is created by the sinus beats measures a simple multiple of an ectopic period.

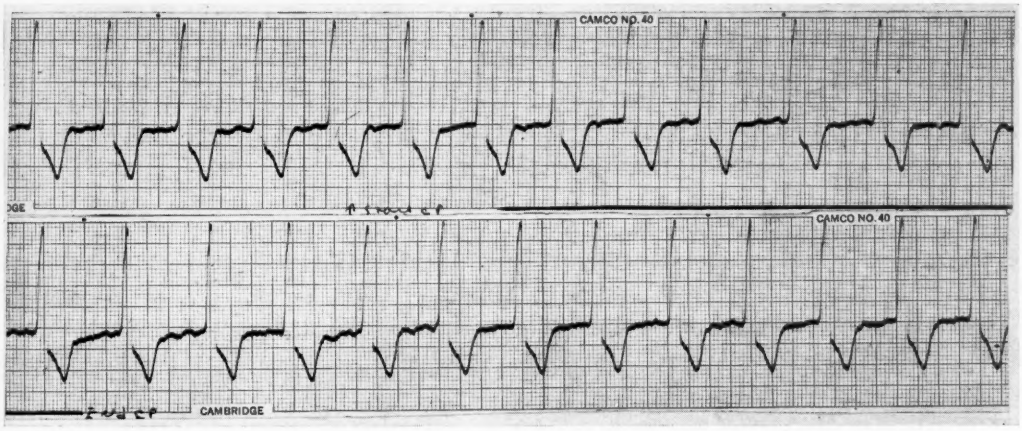

Fig. *7*. Observation 5. The tracings are continuous. Pressure on the carotid sinus, as indicated by the horizontal black line at the bottom of the tracing, slows the ectopic ventricular rhythm.

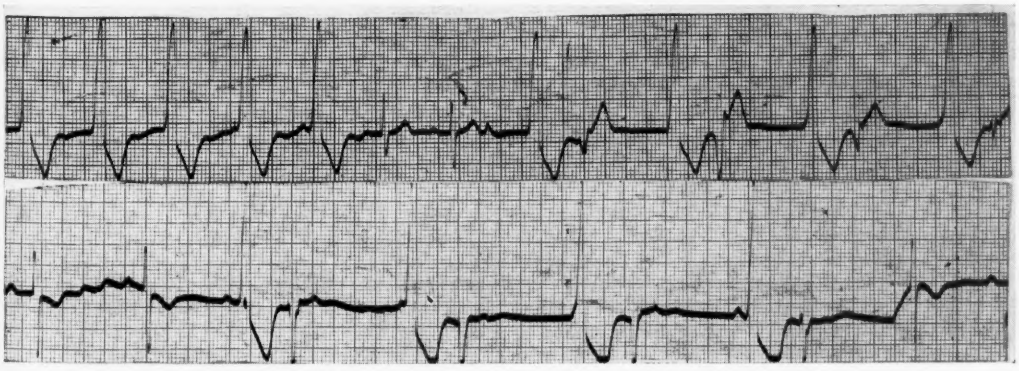

Fig. *8*. Observation 5. Carotid pressure during sinus rhythm causes the appearance of a slow ectopic rhythm with extrasystoles which appeared bound only to the ectopic beats and never to sinus beats.

first the ectopic interval as measured just before and after the sinus beats and then the duration of the pause between two ectopic beats filled by sinus beats.

Figs. 7 and 8 show the effect of carotid sinus pressure. Slowing is demonstrated in *A* and *B* of Fig. 7, in which the interectopic interval increases from 72 to 85 during right carotid pressure (*black line*) and returns to 72 upon the release of pressure. (*A* and *B* of Fig. 7 are continuous.)

The other effect of carotid pressure, the appearance of extrasystoles with fixed coupling to the ectopic beats, is seen in Fig. 8. In *A* of Fig. 8, after an ectopic tachycardia with an interval of 71, carotid pressure elicits ventricular extrasystoles. The ectopic interval measures 132, whereas the interval between the extrasystole and the following ectopic beat is 82 to 84. On the next day, carotid pressure during sinus rhythm (tracing *B*) again evoked an ectopic rhythm, with extrasystoles bound only to the ectopic beats. The interval between ectopic beats is 161 to 168; the postextrasystolic interval is 113. Similar extrasystoles, bound only to the ectopic beats, appeared on two subsequent occasions during carotid sinus pressure.

Observation 6. Another example of parasystole was noted in a 22-year-old woman with a pulmonary stenosis and effort angina. When the patient received no medication, the electrocardiograms usually showed ectopic ventricular beats interrupted by sinus beats. The ectopic interval of 68 (Fig. 9) represents a rate of 86; whereas the rate of the sinus beats, which reflect a marked right ventricular hypertrophy, is 92 per minute. Both rhythms dominated the ventricles for a few beats simultaneously, with the frequent appearance of combination beats. Intervals between ectopic beats separated by sinus beats were always a multiple of the interval between two successive ectopic beats.

In Fig. 10, taken after the patient had been without medication for 10 days, the ectopic intervals continue to be a multiple of the shortest interectopic distances. In this tracing the ectopic intervals vary between 84 and 88. The sinus rate is 75, with a P-P interval of 80. In Lead I (Fig. 10) the ectopic intervals measure 170, 176, 88, and 164; and in Lead II they measure 80, 160, 254, 160, and 164—all multiples of the shortest ectopic interval.

On occasion, the parasystole would disappear without the patient having received medication, and extrasystoles would appear with fixed coupling. In these instances the first interectopic interval was always shorter than the succeeding ones. Quinidine and digitalis abolished the parasystole and led to a bigeminal rhythm with fixed coupling.

Observation 7. Fig. 11, registered in Lead III, was obtained from a 93-year-old woman with coronary sclerosis. In addition to an atrioventricular block the tracing shows ectopic beats with intervals measuring, successively, 164, 52, 156, and 156 (3×52). This measurement suggests an ectopic rate of 115 per minute, corresponding to the shortest interectopic intervals of 52. The longer intervals, which are multiples of this distance, could easily be attributed to an exit block.

Observation 8. This 89-year-old man complained of exertional dyspnea, anorexia, meteorism, and an irregular pulse. Mildly diabetic (on 18 units of NPH insulin daily), he had sustained an anterior-lateral wall myocardial infarction 6 years previously, at which time ventricular beats with varying coupling were noted. Prior to the registration of the electrocardiograms discussed below (Figs. 12 and 13), his physician had administered 0.1 Gm. of digitalis daily, hydrochlorothiazide, and ammonium chloride.

Fig. 12 shows numerous ectopic beats interrupting the sinus beats. The latter exhibit a P-R interval of 0.25 second and the pattern of left ventricular hypertrophy. The intervals between the ectopic beats in tracing *A* (Lead I) are 154, 102, 167, 85, 162, 90, and 180; in *B* (Lead II) they are 126, 42, 84, 250, and 254; in *C* (Lead aV_F) they are 49, 74, 127, 46, 78, and 246; in *D* (Lead V_5) they are 40, 86, 126, 58, 69, 244, and 254; and in *E* (Lead II) they are 268, 221, 47, 230, 41, and 127. These intervals suggest that a center which forms impulses at a rate of 150 per minute (as indicated by the interectopic interval of 40) functions with a 2:1, 3:1, and 4:1 exit block to explain the long intervals. Another feature of parasystole, the combination beat, is seen in the fourth ventricular complex of tracing *B*.

Occasionally, impulses formed in the ectopic center are conducted with a delay to the ventricle so that the interectopic interval is slightly prolonged. The following interval becomes proportionately shorter. Thus, in *C* and *D* of Fig. 12 the sum of a short interval and the succeeding consecutive long ectopic interval equals the sum of the longer preceding or following intervals. The sum of these intervals in Fig.

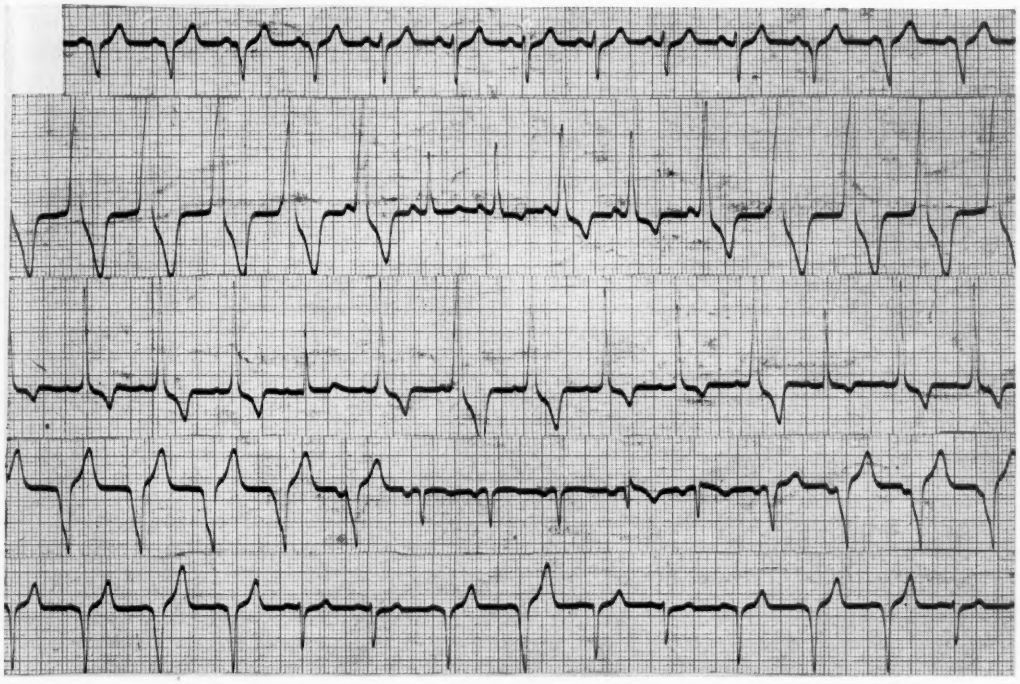

Fig. *9*. Observation 6. Simple parasystole with a rapid ectopic center. The sinus beats show evidence of right ventricular hypertrophy. The tracings were taken in the three standard leads, followed by Leads aV_R and aV_L.

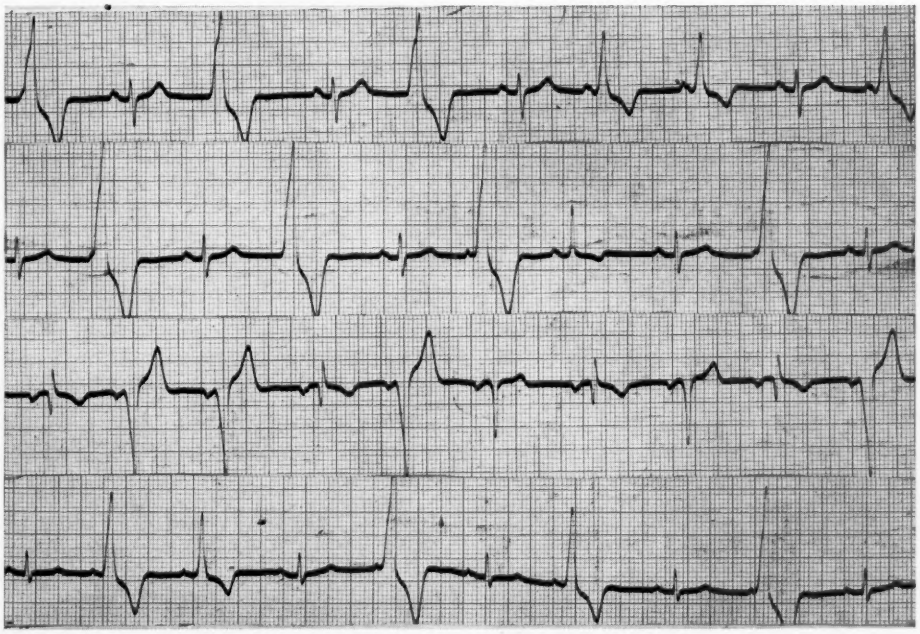

Fig. *10*. Observation 6. The tracings were taken in Leads I, II, aV_R, and aV_F. There is simple parasystole with combination beats.

Table II. *Summary of data obtained in the 8 instances of parasystole with a rapid rate of the ectopic center*

Observation	*Age (yr.)*	*Diagnosis*	*Rate*	*Salient features*
1.	50	Coronary sclerosis	109	Rapid ectopic center protected from sinus beats
2.	67	Inferior wall infarction	109–115	Rapid ventricular center protected from sinus rhythm
3.	88	Coronary sclerosis; atrial fibrillation	96–82 94–83 158	Exit block
4.	48	Hypertension; hemiplegia	142	Exit block, 2:1
5.	80	Coronary sclerosis	76–82	Carotid sinus pressure slowed ectopic rate 83-71 and produced extrasystoles bound to automatic beats
6.	22	Pulmonary stenosis; effort angina	86	Parasystole
7.	93	Coronary sclerosis	115	
8.	89	Coronary sclerosis	150	Exit block

12,*C* totals 123, 127, 124, and 246 (2 × 123). These and similar calculations observed in many of the long tracings recorded in this patient demonstrate that the formation of ectopic impulses takes place in a rapidly acting parasystolic center.

Of great interest and importance in this patient is the inhibition of the sinus beats and the consequent emergence of the full ectopic rhythm by carotid sinus pressure. Two observations with carotid pressure taken 10 days apart are reproduced in the pairs of continuous tracings of Fig. 13, *A* and *B* and *C* and *D*. Although the duration of carotid pressure is roughly indicated by the horizontal black line, pressure was actually applied 3 seconds before the black line registered. Seven additional applications of carotid pressure produced the same effect, viz., inhibition of sinus beats, save for occasional P waves, and the development of an ectopic rhythm free from any disturbance. Here again, as in Fig. 12, short and long interectopic intervals occur. The successive interectopic intervals in *A* and *B* of Fig. 13 measure 261, 44, 84, 129, 79, 41, 127, 126, 126, 126, 127, 51, 73, 124, and 248. In *C* and *D* of Fig. 13 these intervals measure 41, 83, 128, 56, 65, 122, 58, 60, 123, 43, 80, 123, 129, 124, 40, 78, 124, 41, 80, and 246. If, as in Fig. 12, we add the short and the following ectopic intervals, we obtain the following successive intervals: 261 (2 × 130.5), 128, 129, 125, 127, 125, 126, 126, 127, 124, 124, 248 (2 × 124). In Fig. 13 the intervals obtained in the same manner are: 124, 128, 121, 122, 128, 123, 123, 123, 129, 124, 128, 124, 121, and 246 (2 × 123).

This study illustrates both the occurrence of a rapid ectopic parasystolic center exhibiting a 2:1 and 3:1 exit block and the emergence of a full ectopic rhythm during carotid sinus pressure. The conduction of some of the ectopic impulses is delayed in the ventricle so that beats which appear late are followed by a correspondingly shortened interval.

Discussion

These 8 observations, summarized in Table II, present examples of parasystole with rapid rates of formation of impulses in the ectopic center. In some instances, as in Observations 3, 4, 7, and 8, a 2:1 and 3:1 exit block is evident. Ectopic formation of impulses in the ventricles, even with a slow sinus rate, leads to a ventricular paroxysmal tachycardia if the ventricular impulses are conducted in reverse manner to the atria or if the rate is rapid. Simple parasystole may develop in the absence of reversed conduction, provided that the ectopic rate is rapid and exit block exists.

That parasystolic centers with a rapid rate occur is borne out not only by these observations but by a review of reports in the literature. Rapid rates were noted in one of the original papers on parasystole,[9] although the interpretation of these cases has been questioned. In 1932, Faltitschek

and Scherf,[4] reviewing 11 cases of parasystole, found that in 2 instances the rate was over 80 per minute, and in the other cases, between 34 and 61 per minute. Vedoya[16] observed a patient with a parasystolic rate between 133 and 138 during sinus rates of 109 to 133. Katz and Pick[7] described a patient with a sinus rate of 75 to 95 whose ectopic rate was 88 (see their Fig. 196). Gaspary[5] recorded a parasystolic rate of 120. In another observation[8] the rate of an ectopic atrioventricular nodal parasystolic center increased from 83 to 166, proving the presence of a 2:1 exit block.

The inference that a 2:1 or 3:1 exit block obtains in most cases of parasystole

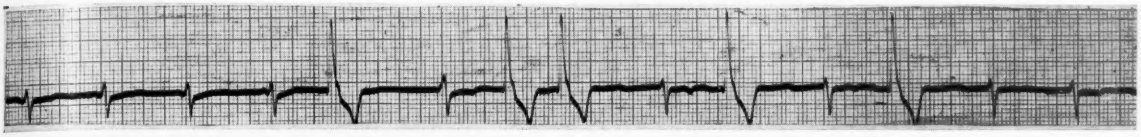

Fig. *11.* Observation 7. Ectopic beats in Lead III, with ectopic intervals of 164, 52, 156, 156, and 156. This suggests that the longer intervals are the expression of a 3:1 exit block.

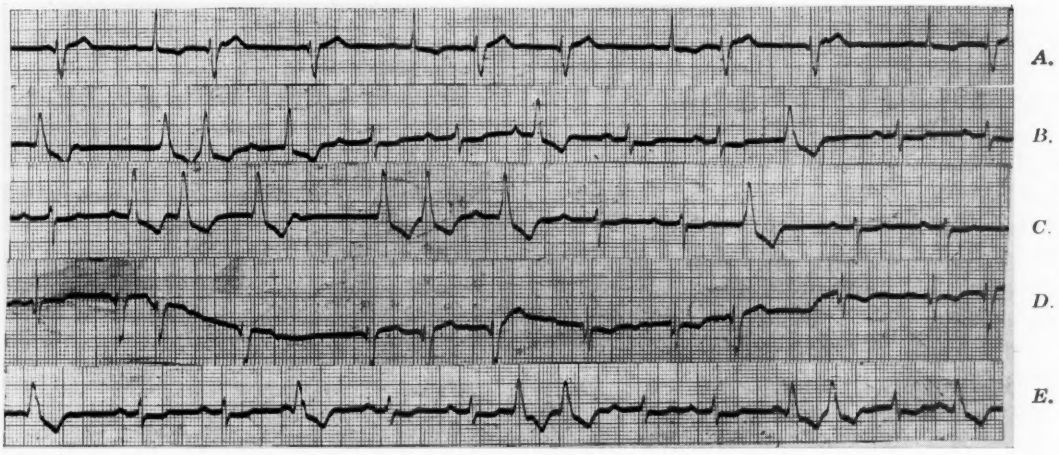

Fig. *12.* Observation 8. Tracings *A* through *E* represent Leads I, II, aV_F, V_5, and II. The tracings show parasystole with exit block. Details are discussed in the text.

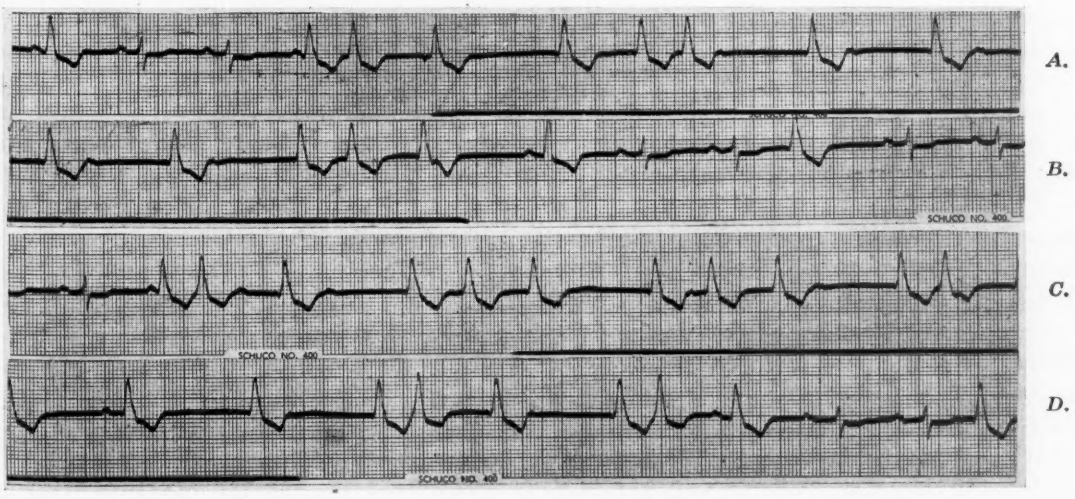

Fig. *13.* Observation 8. All tracings were recorded in Lead II. *A* and *B*, as well as *C* and *D* are continuous. Carotid sinus pressure in both pairs of tracings suppresses the sinus rhythm and permits the undisturbed appearance of the parasystolic rhythm. Details are discussed in the text.

obviates the necessity of postulating the presence of a protection block. A sudden doubling of the ectopic rate, even if only for one beat, as in Observations 3, 4 and 7, and the rates noted in animal experiments quoted above suggest that at least in some instances of parasystole the actual rate of formation of impulses is rapid. Exit block merely makes it appear that the automatic rhythm is slow. If a center fires off impulses rapidly, it will be refractory to other impulses. We have no way of knowing whether all ectopic intervals measured directly in these tracings are not the expression of a 2:1 block. It is also possible that the ectopic center develops oscillatory potentials with a rate of about 300 and that only every second one reaches threshold values. Thus, in explaining parasystole, recourse need not be taken to theories which contradict known physiologic laws.

In experiments on dogs, parasystole can be provoked by focal application of veratrine on the ventricles of the exposed heart,[12,13] and by short mechanical or electrical stimulation of the ventricles after previous intravenous administration of quinine and atropine. In all these instances the rate of the ventricular parasystolic center is rapid.

Several observations indicate that the parasystolic center differs from the physiologic deeper ventricular centers. The latter function with a slow rate of automatism, as demonstrated by escaped beats and idioventricular rhythms. The rate in the observations described in the present paper is too rapid to be considered as the expression of a physiologic but protected automaticity. Conversely, in atrioventricular or nodal parasystole the rate may be far slower than the anticipated rate of formation of impulses at these centers. Consequently, these forms of parasystole must also be assumed to be caused by an abnormal kind of impulse formation.[11]

Another observation which sets the parasystolic center apart from the physiologic activity of deeper centers is the slowing of the ectopic rhythm in parasystole by carotid sinus pressure.[6] This slowing of parasystolic centers suggests that they are very sensitive to small amounts of acetylcholine. Normal ventricular centers rarely respond to the vagal effect of carotid pressure.[3]

The appearance of ventricular extrasystoles bound only to automatic ectopic beats and not to conducted beats, as in Observation 5 after carotid sinus pressure, has been described before[15] but remains unexplained.

All patients described in this presentation suffered from organic heart disease.

The presence of a center of rapid impulse formation in conjunction with a supernormal phase of excitability may lead to extrasystoles with constant or almost constant coupling.

Since this paper was submitted for publication, 3 more instances of parasystole with sudden temporary doubling of rate were observed.

Summary and conclusions

Parasystole was observed in 8 patients, with the rate of the ectopic center varying between 86 and 150 beats per minute.

In 3 instances the rate of the ectopic center suddenly doubled for one beat, suggesting the presence of a 2:1 exit block in the other tracings. In one patient a 3:1 exit block existed.

The possibility is discussed that the ectopic rate in many clinical instances of parasystole actually is high, and that a 2:1 or 3:1 exit block gives the impression of a slow ectopic center.

Assuming the presence of a rapid ectopic center, we need not consider the hypothetical action of a protection block.

One patient showed a clear exit block. Another patient revealed slowing of the automatic rate of the ectopic center by carotid sinus pressure and the repeated appearance of ventricular bigeminal rhythm during carotid pressure, with the extrasystoles bound only to the ectopic beats and not to sinus beats. In addition to 2:1 and 3:1 exit block, one patient showed a delay of the spread of the ectopic impulses from the center to the ventricles.

These observations make it improbable that the ectopic activity in parasystole represents simply the expression of the normal automaticity of a ventricular center. An abnormal, rapid kind of impulse formation seems more probable. Therefore, the separation of parasystole from rapid ectopic tachycardias is less sharp; the presence or absence of an exit block makes the difference.

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The genesis of the normally split first heart sound

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In spite of the remarkable progress in phonocardiography—including intracardiac and extracardiac techniques—there is still some disagreement concerning the genesis of the two major components of the normally split first heart sound. This is emphasized in a recent paper by Luisada.[30]

Without regard to pathologic conditions (i.e., "systolic clicks"), two contradictory theories are under discussion to explain the normally split first heart sound. Although there is general agreement in the interpretation of the *first major component* of medium-high-frequency vibrations, which is related by nearly all authors to closure of the left-sided atrioventricular valve (or to the normally simultaneous rapid rise in left ventricular pressure), some authors, since Potain[39] (1866), explain the *second major component* as being due to closure of the tricuspid valve (Dock,[6] Wolferth and Margolies,[46] Leatham,[22-24] McKusick,[33,34] Reinhold and Rudhe,[41] Braunwald and Morrow[3]), in contrast to another group which believes it to be due to opening of the aortic valve or to left ventricular ejection (Orias and Braun-Menendez,[37,38] Rappaport,[40] Luisada,[28-30] Minhas and Gasul[35]).

The conclusions are based partly on hypothetical grounds, clinical observations, and experimental facts. The reported data fall into two groups: (1) temporal relationship between the sounds recorded in the extracardiac or intracardiac phonocardiograms and other cardiac events, i.e., events in the cardiac chambers or the great vessels which are recorded in electrocardiograms, electrokymograms, pulse tracings, or pressure measurements (but the coincidence of two events does not prove their causal connection and, therefore, may be misleading); (2) correlations between the site of maximum intensity of the different components of the first heart sound and the location of the sound-producing structures.

In our study we tried to approach the problem by measuring: (1) the *intensity distribution* (and distance) of the two main components of the split first heart sound at five different points on the precordium (2.RIS, 2.LIS, 3.LIS, 4.LIS, apex), in a statistical analysis of data from children who were 2 to 12 years of age; and (2) the *intensity variations* of the afore-mentioned vibrations under functionally altered conditions, i.e., respiration and Valsalva maneuvers.

Method and material

Simultaneous electrocardiograms and phonocardiograms were recorded by means of an Atlas four-channel oscillograph on photosensitive paper, using the Maass and Weber method[31,32] which operates with 5 different high-pass filters. The nominal frequencies and the slope of attenuation are as follows: t = 35 c.p.s., 7.5 decibel per octave; m_1 = 70 c.p.s., 18 db./octave;

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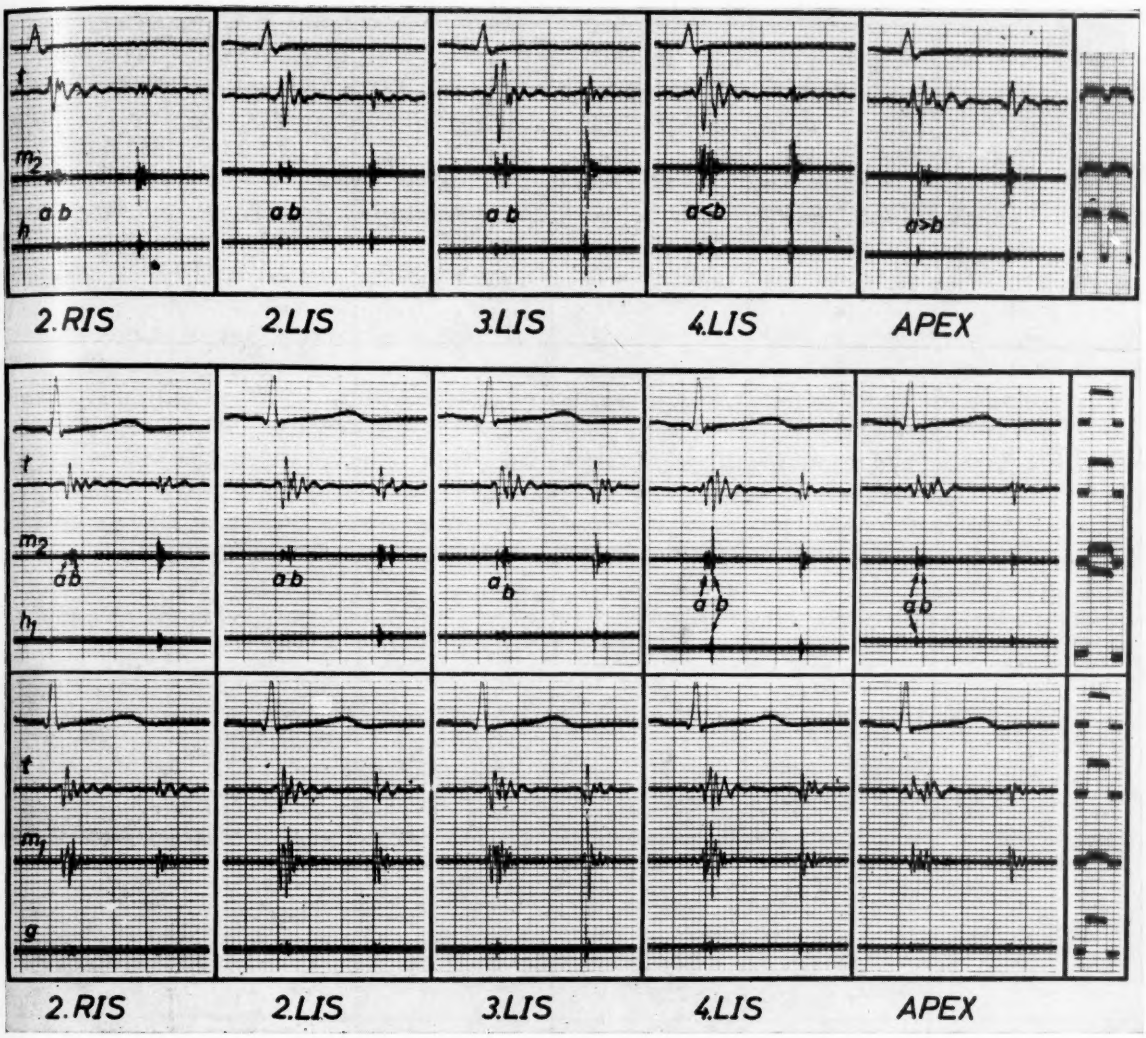

Fig. *1*. Representative electrocardiograms and phonocardiograms from two children, which show the typical intensity distribution of the two main components (*a*,*b*) of the physiologically split first heart sound in different frequency bands and at five locations (see under *Method*). *Above:* Fifteen-year-old girl. Same case as in Fig. 4. *Below:* Ten-year-old girl; whole frequency range (*t:* low; m_1*:* medium-low; m_2*:* medium-high; h_1*:* high; *g:* "earlike"). Distance between the heavy vertical lines = 0.1 second. On the right, calibration is by means of the 1-millivolt ECG signal.

m_2 = 140 c.p.s., 24 db./octave; h_1 = 250 c.p.s., 24 db./octave; g = "earlike" = 140 c.p.s., 12 db./octave.

A. Investigations on intensity distribution. In the first part of the investigation we took 60 tracings out of a material consisting of some 2,000 phonocardiograms, all of which were recorded (1) in five frequency bands, (2) at five different locations (2.RIS, 2.LIS, 3.LIS, 4.LIS, and apex), (3) at a paper speed of 100 mm. per second, and (4) with the subject in the recumbent position (for example, see Fig. 1). The selection was arbitrary, with the exception that pathologic cases with systolic clicks were excluded.

The recordings were made with constant sensitivity at the five different locations in each individual case, but the amplification was adapted to the varying intensity of heart sounds in the five frequency bands in each child. The amplification of the four channels was calibrated by means of the 1-millivolt (mv.) ECG signal. Therefore, the amplitudes of the vibrations could be expressed in relative values (mv.), thus allowing an interindividual comparison within each frequency range. The intensity

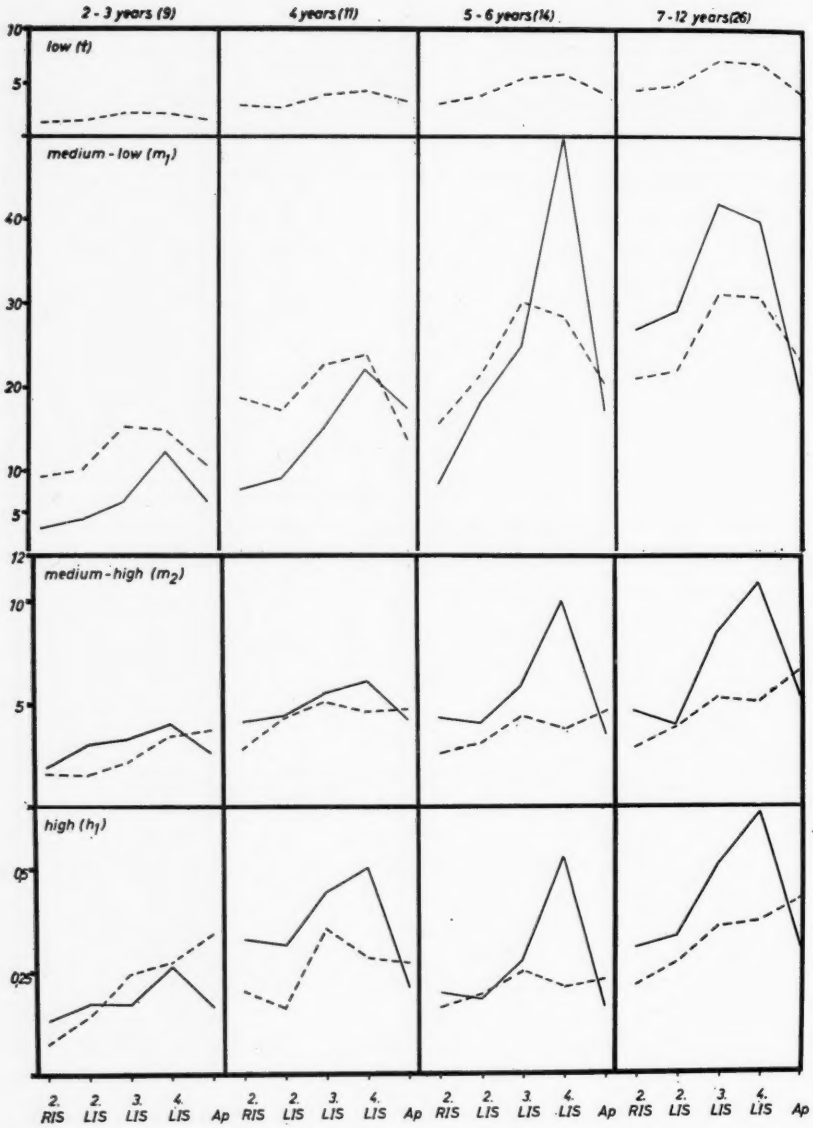

Fig. 2. Graphic representation of the average amplitudes of the first (– – –) and second (——) main components of the split first heart sound in the different age groups, frequency bands, and areas of recording (abscissa). Numbers in parentheses after age show the number of cases.

relations between the five frequency bands could not be established. At all locations and frequency bands where splitting was obvious, at least five consecutive amplitudes of the vibrations under discussion were measured, in millimeters (mm.), and the means values were taken for further analysis.

The material was first divided into five groups on the basis of age of the subjects, but the two groups of older children were then put together because there was no evidence of age differences. The final distribution is as follows: 2-3 years of age, 9 cases; 4 years, 11 cases; 5-6 years, 14 cases; 7-12 years, 26 cases. Within each age group the means of both components of the split first heart sound were evaluated for each location and frequency band. Although the amplitudes of all heart sounds were measured, this paper deals only with the complex of the first heart sound. The full results will be published elsewhere.[16]

In addition to the amplitudes, the time of onset of the two major components of the first heart sound in respect to the beginning of the electrocardiogram (the Q wave) was measured. The following abbreviations are used: SI: First heart

sound complex. AIa: Amplitude of the first major component of SI. AIb: Amplitude of the second main component of SI. Q-Ia: Interval between the Q wave of the ECG and the beginning of the first component of SI. Q-Ib: Interval between the Q wave of the ECG and the beginning of the second component of SI. Ia-Ib: Individual time difference between the two main components of SI.

B. Respiration experiments. In some children with clearly split first sounds, continuous recordings of the medium-frequency and high-frequency phonocardiogram were made simultaneously with the pneumogram, the electrical transformed spirogram, or records of the esophageal pressure for at least 1 to 1½ minutes (about 100 to 150 consecutive heart cycles) during quiet respiration. As already pointed out by Dornhorst and Leathart,[7] the pneumograms correlate well with the spirograms, and are therefore a useful reference of the frequency, phase, and depth of respiration.

The consecutive respiratory cycles were plotted one upon the other by setting the maximum inspiratory amplitudes of the respiratory records at 100 per cent. When this is done, heart sounds occur in all parts of the respiratory cycle, allowing a continuous band to be drawn from the amplitudes of the first, as well as from the second, component of the split first heart sound that reflects the different respiratory variations of these components.

C. Valsalva maneuvers. The straining procedure was performed with the subject in the recumbent position blowing against a mercury manometer, which was connected in parallel with the Statham strain gauge, or against the closed glottis, and the intraesophageal pressure was recorded with the Statham transducer. Pressures of from 20 to 60 mm. Hg were held for 10 to 20 seconds. The maneuver, which we often use as an aid in the differentiation between left-sided and right-sided murmurs (according to Zinsser and Kay[47]), can be performed, with some patience, in most children over 4 years of age.

The pressure curves were recorded synchronously with the heart sound in different frequency bands by means of the above-described apparatus, using a paper speed

Table I

Age	*N*	$\bar{x} \pm S\bar{x}$	*S.D.*	*Difference**	S_D	*Diff./*S_D	*p*
QIa:							
2–3	47	48.1 ± 0.55	3.7	5.0	0.96	5.2	<.000001
4	58	53.1 ± 0.72	5.5	−0.6	0.92	0.6	<.55
5–6	80	52.5 ± 0.58	5.2	2.7	0.5	5.4	<.000001
7–12	192	55.2 ± 0.55	7.0				
2–12	377	53.4 ± 0.33	6.4				
QIb:							
2–3	40	66.8 ± 1.12	7.1	5.3	1.13	4.6	<.00001
4	57	72.1 ± 0.83	6.2	2.4	0.97	2.5	<.02
5–6	77	74.5 ± 0.57	5.2	4.1	0.83	4.9	<.000001
7–12	163	78.6 ± 0.63	7.7				
2–12	337	75.2 ± 0.42	7.8				
Ia–Ib:							
2–3	39	18.8 ± 0.88	5.5				
4	52	18.9 ± 0.47	3.4	2.7	0.59	4.6	<.00001
5–6	72	21.6 ± 0.34	2.9	1.3	1.0	1.3	<.2
7–12	153	22.9 ± 0.29	3.7				
2–12	316	21.5 ± 0.23	4.1				

*Difference between $\bar{x}$ values.

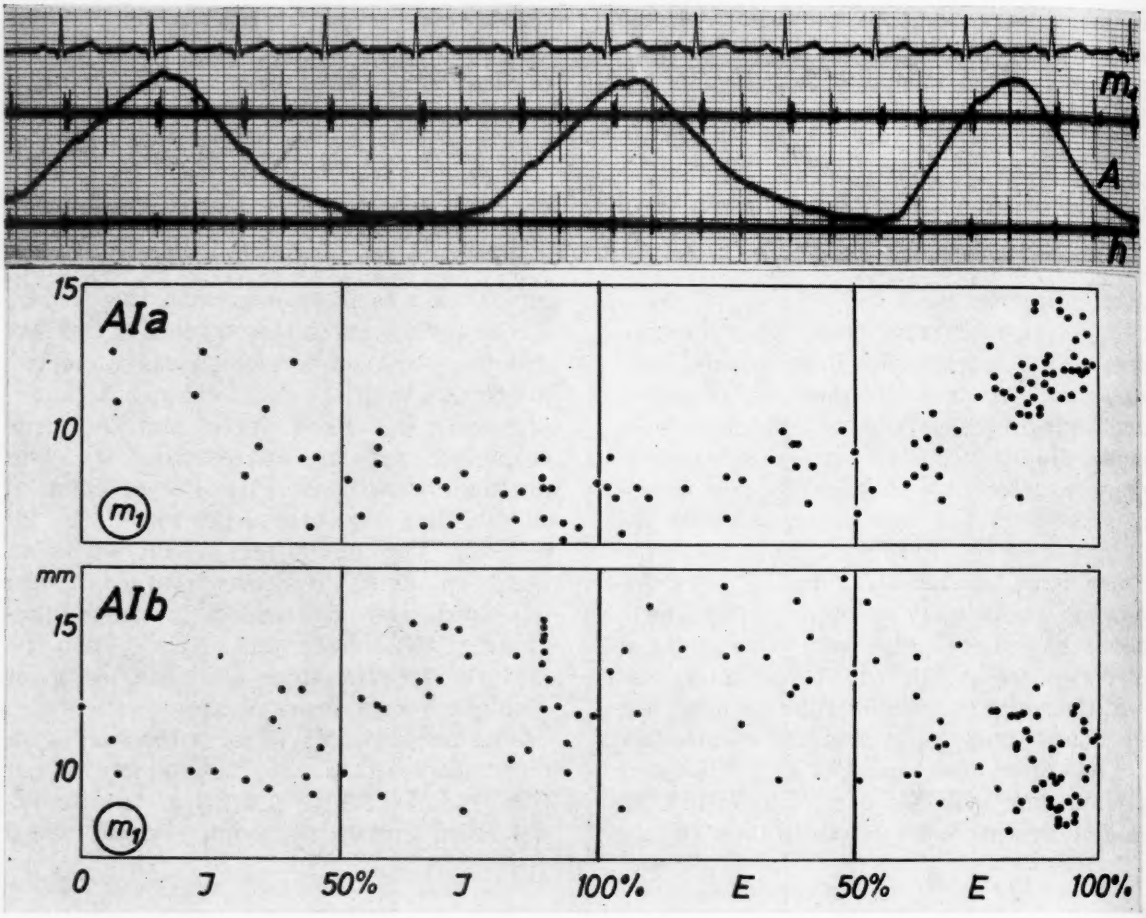

Fig. 3. *Above:* Part of the original recording which shows the ECG, phonocardiogram, and pneumogram taken from a 6-year-old boy. Distance between the heavy vertical lines = 0.1 second. *Below:* Graphic evaluation of the amplitudes (given in millimeters) of the first (*AIa*) and second (*AIb*) components of the split SI (ordinate) against the phase of respiration, in per cent, of maximum inspiration or expiration (= 100 per cent) according to the principles described in the section on *Method. I:* Inspiration. *E:* Expiration.

of 100 mm. per second. Special attention was paid to Phases III and IV according to Hamilton and associates.[14]

Results

A. The intensity distribution of the two major components of the first heart sound along the anterior chest wall is represented in Fig. 2. The average amplitudes of the two components are plotted in relative terms (millivolts) on the ordinate, versus the area of recording for each frequency band and age group. In the low-frequency band the differentiation between the two components of the first sound has not been tried, although it is often possible to separate right-sided and left-sided events in this tracing.

1. As can be seen, there is a general tendency for all measured components to *increase with age,* if comparable values (same frequency band and area) are considered. At least this holds for the points of maximum intensity.

2. The *points of maximum intensity* are, in nearly all instances, different for both components of the first heart sound. Whereas the second component (AIb) has, with one exception, its greatest amplitude at the fourth left intercostal space, the behavior of the first group of vibrations is different. In the medium-high-frequency and high-frequency bands there is a fairly uniform pattern. The lowest values are at the second right intercostal space. They show a gradual increase along the left sternal border, reaching their maximum at the apex. In the medium-low-frequency

band the point of maximum intensity is at the third or fourth intercostal space, thus reflecting the behavior of the maximum amplitudes in the low-frequency range.

3. The *intensity relations between both components* at different areas are the most interesting point. Although the second component (AIb) has the greater intensity along the left sternal border, especially in the medium-high-frequency and high-frequency bands (and also in the medium-low-frequency range of the older children: those 5 to 12 years of age), the relationship changes at the apex. Here the first component of the split SI predominates. This observation, already described in adults by Leatham,[22] is, therefore, *a constant feature in all of the children included in this study.*

4. The *average time interval* from the beginning of the Q wave to the onset of the first and second components of the split first sound in the various age groups, and the average distance between both components, calculated from the individual time difference (Ia-Ib), are given in Table I. The average values within the whole group are 53.4 ± 0.3 msec. (S.D. 6.4) for the first component and 75.2 ± 0.42 msec. (S.D. 7.8) for the second component of the first heart sound. As can be seen, these values show a tendency to increase with age, a finding which is significant in most instances. The average splitting interval is 21.5 ± 0.2 msec. (S.D. 4.1). The differences between the younger children (2-4 years) and the older children (5-12 years) are also significant ($p < .001$).

B. The respiratory variations of the amplitudes of both components of the split first heart sounds in two typical patterns are illustrated in Figs. 3 and 4. The upper part of each illustration shows a section from the original phonocardiograms, which are evaluated below according to the principles described under *Method.*

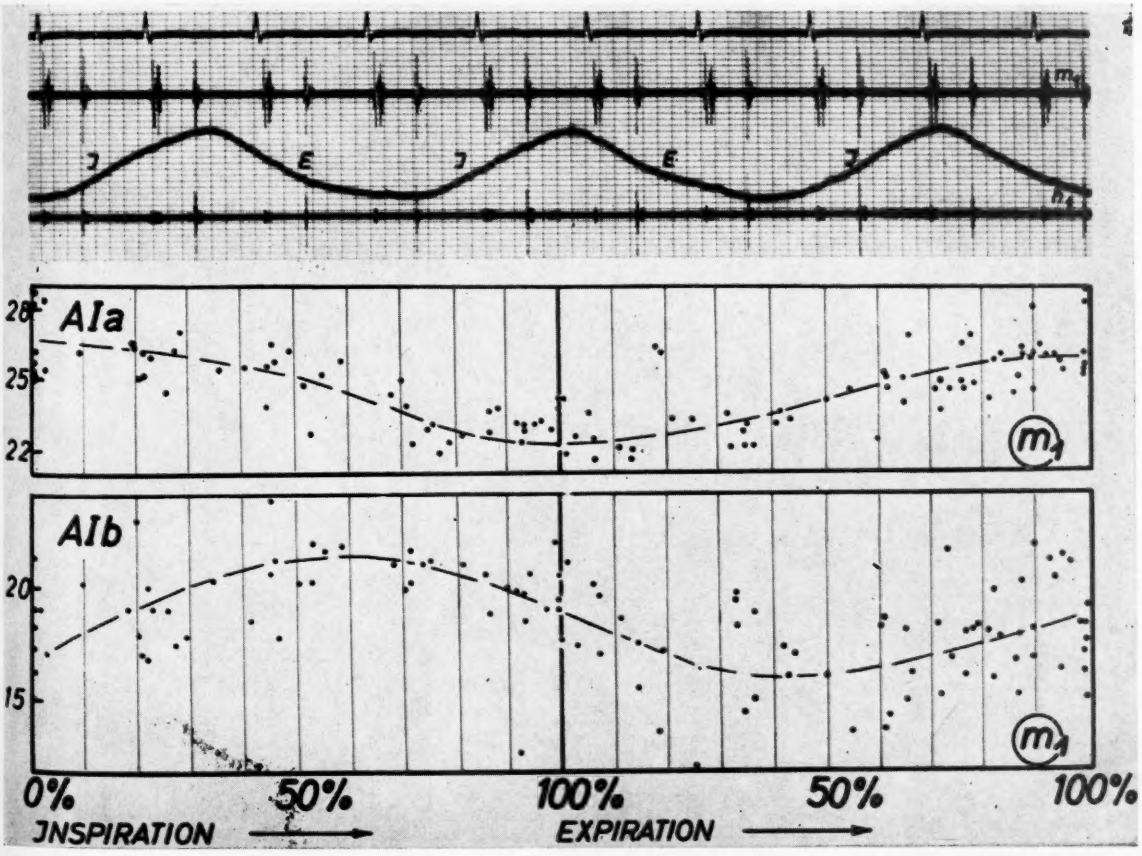

Fig. 4. Respiratory variations of both components of a split SI. Method of representation is the same as that in Fig. 3. Same girl as in upper section of Fig. 1. The amplitude of AIb reaches its peak during inspiration, somewhat earlier than in Fig. 3. Inspiratory decrease in intensity of AIa as in Fig. 3. *I*: Inspiration. *E*: Expiration.

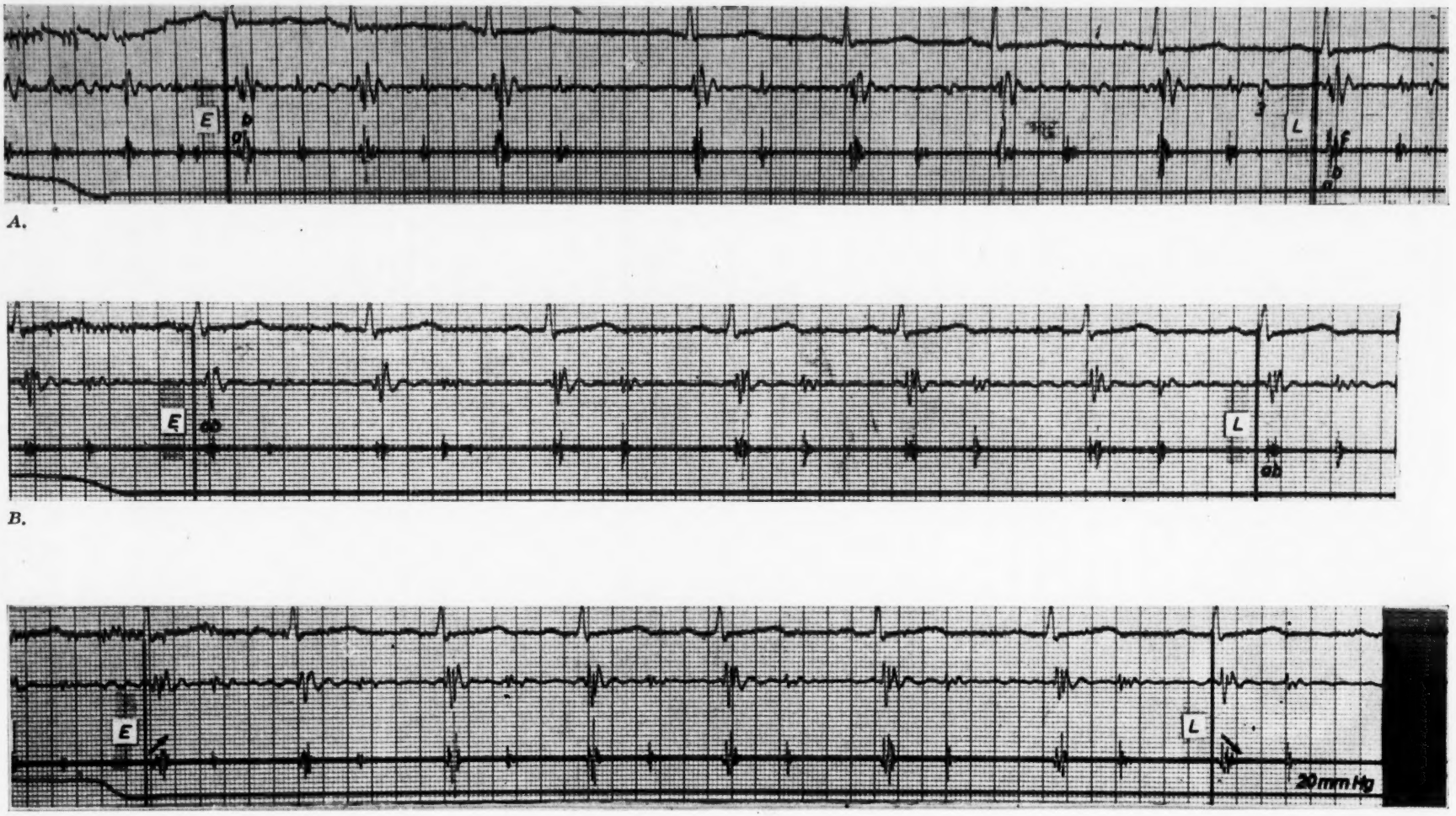

Fig. 5. Three examples which show the electrocardiogram, phonocardiogram, and oral pressure curve at the end of, and just after, the straining procedure. In the early poststraining period the initial component of the first sound complex (*a*) is small, whereas the second component (*b*) predominates. With the following heart cycles the first component tends to increase, whereas the second component decreases, so that the amplitude relationship changes. *E* and *L* indicate, respectively, the early and late poststraining first sound complexes, which are augmented photographically and put one below the other in Fig. 6, using the electrocardiogram (black lines) as a time reference.

The striking feature is the different behavior of the two components of the split first sound during the phases of respiration. Whereas the initial component (AIa) decreases in intensity during inspiration, the second group of vibrations shows, in the first case, much greater variations, but the intensity rises, averagewise, during inspiration and falls during the second part of expiration. In the second case, which is the same as in the upper part of Fig. 1, the intensity of the second component (AIb) reaches its peak somewhat earlier during inspiration and decreases at the beginning of the expiratory phase. As established elsewhere, this behavior cannot be explained by extracardiac factors, such as varying interposition of lung tissue, although respiratory modifications in the conduction of sound may interfere with changes in the generation of sound.[15] These conclusions are based mainly on the fact that the variations of those factors which influence the conduction of sound—such as lung volume and tension, intrathoracic pressure, displacement of the heart and diaphragm—are not "in phase" with the changes in intensity of heart sounds.

The temporal shifting of both components during respiration is difficult to measure exactly, and is therefore outside the scope of this publication. In lesser degrees of splitting, both components tend to merge, particularly in the inspiratory phase.

C. Three typical Valsalva experiments are represented in Fig. 5, which is limited to the poststraining Phases III and IV. Immediately after the intrathoracic pressure falls, both heart sounds are still faint, as in the pressure phase. Then the first component of the split first heart sound, including the initial group of the low-frequency tracing, still visible at the end of Phase II, diminishes or sometimes disappears in the early poststraining period (Phase III).

In contrast, the second main component of the split SI rises rapidly after the

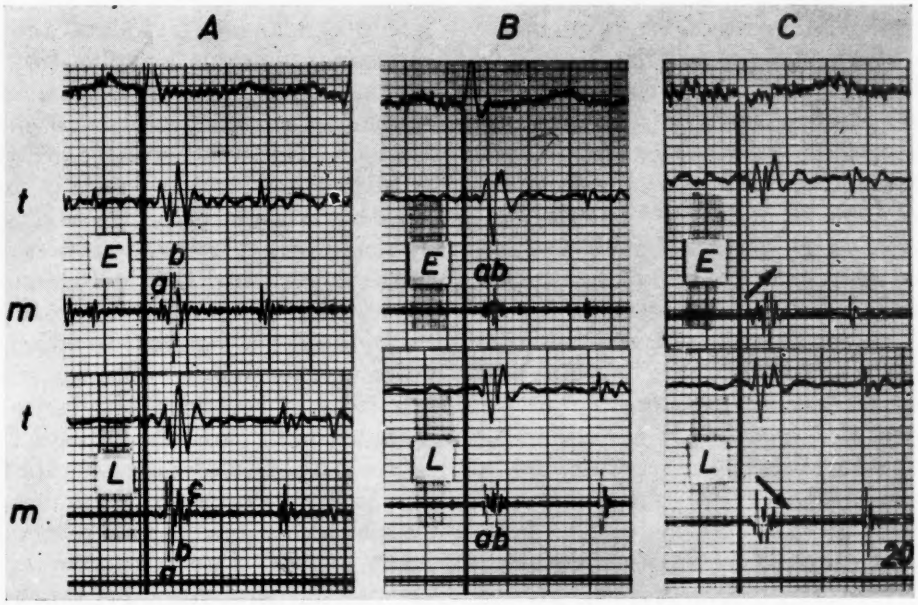

Fig. *6.* Three early (*E*) and three late (*L*) heart sound complexes which are indicated in Fig. 5 (*A*,*B*,*C*) and plotted one below the other, using the ECG (black lines) as a time reference. The changes of both components of the split SI are obvious, especially in the medium-frequency band (*m*). In *A* there is a distinct reversal in the relationship of the amplitudes between *a* and *b*. Besides this, a third vascular component of SI (*c*) appears in the late heart cycle. In *B*, both components are nearly equal in the late poststraining period, whereas the terminal component dominates in the early sound complex. In *C* the early poststraining first sound complex shows a crescendo, and the late complex a decrescendo-like pattern. Note also the shift of the second heart sound in the poststraining phase and the delayed appearance of a marked third sound in *A*.

intrathoracic pressure relaxes. This results sometimes in a (pseudo) delayed onset of SI. With the following heart beats a gradual rise in the initial component (AIa) is associated with a decrease in AIb, which reaches its maximum amplitude during the first two or three poststraining beats. Therefore, after a few beats the initial intensity relation between both main vibratory groups of SI reverses.

In Fig. 6, one early (*E*) and one late (*L*) poststraining first heart sound complex from the same Valsalva experiments illustrated in Fig. 5 are plotted one below the other, with the ECG used as time reference. As can be seen, there are always the above-mentioned changes in intensity, which lead: (1) to a reversal of the amplitude relation between both components of the split first heart sound, if the splitting is distinct and the first component (AIa) is normally predominant at the area of recording (Fig. 6,*A*); (2) to a relative increase of the first component in respect to the second only, whereby the second component remains equal or predominant in the poststraining period, if the second component is normally overwhelming at the area of recording, i.e., 4.ICS (Fig. 6,*B*); or (3) to a crescendo-like pattern of the first sound complex in the early poststraining period, which changes to a decrescendo-like pattern some beats later, if the splitting is not quite distinct (as is often the case in the medium-low-frequency band) (Fig. 6,*C*).

Without regard to the afore-mentioned differences the individual pattern can always be reproduced with a high degree of accuracy under similar conditions.

Variations of the described typical pattern are the consequence of: (1) different duration and intensity of the straining procedure, (2) variable filling of the low pressure system anterior to the left and right heart (congestive failure), (3) variable duration of circulation time in the lung, (4) the degree of reflex vasomotor activity in the systemic (and lung?) circulations.

Hence, the reactions to the Valsalva experiment which are recorded in the phonocardiogram depend on the same factors which influence the hemodynamic response to the straining procedure (Bürger and Michel,[4] Elisberg and associates,[8,9] Gorlin and associates,[13] Hamilton and associates,[14] Howard and associates,[17] Knowless and associates,[19] Lee and associates,[25] Rushmer,[42] Sharpey-Shafer.[44]

The changes in intensity and timing of both components of the *second heart sound* are outside the scope of this article and are described in detail elsewhere (Heintzen[15]).

The *third heart sound* reaches its maximum amplitude during the late poststraining period (Phase IV), which is in accordance with its supposed left-sided origin. This is of interest in so far as the first component of the split SI attains its crest just after the third sound (Figs. 5,*A* and 6,*A*).

Conclusions

To summarize our findings, there is one component of the normally split first heart sound (AIa) which (1) has its point of maximum intensity in the medium-frequency and high-frequency bands at the apex, where it is greater than the other component, (2) decreases in amplitude with inspiration, and (3) reaches its maximum, sometimes overshooting it, in the late poststraining period of the Valsalva maneuver. This is usually the first component of the normally split first heart sound. It appears about 50 msec. after the Q wave of the electrocardiogram.

All of these facts are quite in accordance with the concept that the initial vibrations of the first heart sound have their origin on the left side of the heart, and the medium-high-frequency fraction is related to closure of the mitral valve, for the following reasons. (1) The intensity distribution is identical with that of other vibrations of known left-sided (mitral) origin. (2) The decrease in amplitude with respiration reflects the inspiratory diminution of blood flow to and through the left heart. (3) The late poststraining intensity crest is the consequence of the delayed appearance in the left heart of that blood wave which was accumulated in the venous system during the elevation of intrathoracic pressure.

Finally, the time of onset of the vibrations under discussion coincides with the reversal of the left-sided atrioventricular pressure differential (Braunwald and associates,[3] Luisada[29,30]) and with the first sound vibrations recorded within the left

ventricle (Feruglio,[10,11] Luisada and associates[29]).

The other main component of the split first heart sound (1) has its point of maximum intensity at the lower sternal edge, where it has regularly a greater amplitude than the first component, (2) increases in intensity during inspiration, and (3) reaches its maximum amplitude immediately after the release of pressure in the Valsalva maneuver. This is normally the second main group of vibrations within the first heart sound complex. Its average time of appearance is 75 msec. after the onset of the Q wave of the ECG.

When these results are confronted by the contradictory theories of aortic or tricuspid origin of these vibrations, the facts strongly favor the concept of tricuspid origin. The intensity distribution at the thoracic wall is not that which could be expected from a sound originating in the aorta. Also, the amplitude of the sound due to closure of the aortic valve, not demonstrated here, has another intensity distribution in the same material.

In contrast, the increasing amplitude downward to the lower sternal edge corresponds with the premises which should be fulfilled by a sound originating from the tricuspid valve. The early increase in intensity during the inspiratory and poststraining periods is further evidence for the right-sided genesis of the second main component of the normally split first heart sound. It can reasonably be related to the augmented venous return to the right heart, which is due mainly to thoracic aspiration or is the consequence of the pooling of venous blood during the pressure phase of the Valsalva maneuver. An aortic ejection sound would be expected to have another intensity distribution and to show variations with respiration and the straining procedure which resemble the left-sided hemodynamic changes, but not to behave in the opposite way.

Furthermore, the temporal relationships between the second main group of vibrations and the electrocardiogram are in the same range (75 ± 0.42 msec.; S.D. 7.8 msec.) as the values reported (1) for the delay of the first sound vibrations recorded within the right heart (Moscovitz and associates,[36] Feruglio[10,11]), and (2) for the rapid rise in right ventricular pressure or closure of the tricuspid valve (Coblentz and associates[5]).

Finally, the time difference between both main vibrations of the split SI (21.5 ± 0.2 msec.; S.D. 4 msec.) means that in about 95 per cent of the cases investigated the splitting interval ranges from 13.5 to 29.5 msec., which is compatible with the measured values for the normal asynchronism of right-sided and left-sided dynamic events in animals and men (Katz,[18] Laszt and Müller,[20] Braunwald and associates,[1,3] Samet and associates,[43] Gribbe and associates[12]). This interval is too short to represent the isometric contraction phase of the left ventricle, which lasts about 50 msec. (Wiggers,[45] Braunwald and associates,[1] Luisada and associates[29]).

If the complex of the first heart sound consists of three distinct groups of vibrations (which is not a rare finding in our material), that component which has, according to its intensity distribution, timing, respiratory and straining variations, the characteristics of the sound due to closure of the tricuspid valve is the second group of vibrations, and is followed by a third one, which has the qualities of a vascular or ejection sound. This third group of vibrations appears about 50 msec. after the initial component of the first heart sound.

So, there is no doubt that, at least in the age group under study (2 to 12 years), the second main component of the normally split first heart sound is of right-sided (tricuspid) origin. The normal splitting of SI is due, therefore, to asynchronous closure of the atrioventricular valves or to the time difference between rapid rise in pressure in the two heart chambers.

Summary

1. The intensity distribution along the anterior chest wall, timing, respiratory and poststraining variations of the physiologically split first heart sound, especially in the medium-high-frequency range, has been investigated by means of multiple-filter phonocardiography in children who were 2 to 12 years of age.

2. In 60 children from 2 to 12 years of age the first main component of the split first heart sound has, on an average, its maximum intensity at the apex, where

it is of greater amplitude than the second main group of vibrations.

3. The second component of the split first heart sound has its point of maximum intensity (especially in the medium-high-frequency band) at the fourth left intercostal space and is the dominating vibration along the left sternal border in each age group.

4. The reversal of the intensity relationship between both major components of the split first heart sound from the left sternal border to the apex is a constant feature in the whole group of children included in this study.

5. The average time interval from the Q wave to the beginning of the first main component of the split first heart sound is 53.4 ± 0.33 msec. (S.D. 6.4 msec.); and to the onset of the second main component the interval is 75.2 ± 0.42 msec. (S.D. 7.8 msec.).

6. Both main components of the split first heart sound are normally separated by no more than 21.5 ± 0.23 msec. (S.D. = 4.1 msec.). Therefore, in about 95 per cent of all normal children the splitting interval is shorter than 30 msec.

7. The intensity of both components of the normally split first heart sound as well as the splitting interval increase with age.

8. During inspiration the first component of the split first heart sound decreases in intensity, whereas the second component increases, if respiratory variations of sound conduction (transmission) can be eliminated.

9. During the poststraining period of the Valsalva maneuver the second component of the split first heart sound reaches its maximum amplitude immediately after the release of pressure, whereas the initial group of vibrations is at first small and increases with some delay.

10. The respiratory and poststraining variations of both splitting components reflect the different hemodynamic events of the left and right sides of the heart.

11. The intensity distribution, timing, respiratory and poststraining behavior of the first component of the normally split first heart sound are in accordance with the concept of left-sided (mitral) origin of the vibration, whereas the corresponding data for the second main component of the normally split first heart sound leave no doubt that this vibration is, at least in the 2 to 12-year age group studied, of tricuspid and not of aortic origin.

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The indications for measurement of left heart pressures in mitral and aortic valvular disease

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The assessment of obstruction of the mitral and aortic valves relies on measurement of the transvalvular pressure gradient and simultaneous estimation of the cardiac output. Evaluation is difficult in the presence of mitral or aortic regurgitation because the forward flow across the valve in these circumstances is greater than expected from the cardiac output. The severity of mitral or aortic incompetence may be assessed from the clinical, electrocardiographic, or radiologic evidence of increased left ventricular stroke volume, and additional information is provided by the left atrial or aortic pressure pulses. Regurgitant flow can also be estimated by indicator-dilution methods[1-3] or angiocardiography.[4,5]

An appreciable risk is involved in attempts to measure left heart pressures, and the value of the data obtained must be considered in relation to the morbidity of the procedure. In many situations the information provided by right heart catheterization is adequate. The indications for measurement of left heart pressures are clarified in this report of 133 consecutive cases of mitral or aortic valvular disease which were studied in the past year.

Methods

The techniques used are described in detail elsewhere.[6] Aortic pressure was recorded continuously, using the Seldinger method,[7] and right heart catheterization was performed in each case. Left atrial pressures were obtained via a slotted bronchoscope, which was then removed, leaving the needle in place.[6] Left ventricular pressures were recorded by direct puncture through the anterior chest wall,[8] or by retrograde catheterization, using a Cournand catheter through the right brachial artery.[9] When conditions were constant, pressures were recorded simultaneously on each side of the mitral (Fig. 1) or aortic (Fig. 2) valves, and cardiac output was estimated by the Fick method. The middle of the chest at the level of the second costal cartilage was taken as the base line for pressure measurements.[10] P23Db strain gauges and a four-channel direct-writing Sanborn Poly-Viso were used to record the pressures, which were then replotted on the same scale (Figs. 1, 2, and 3). The content of oxygen in the blood was determined by the Van Slyke method.[11]

The areas of the valves were calculated by using standard orifice formulae,[12] on the

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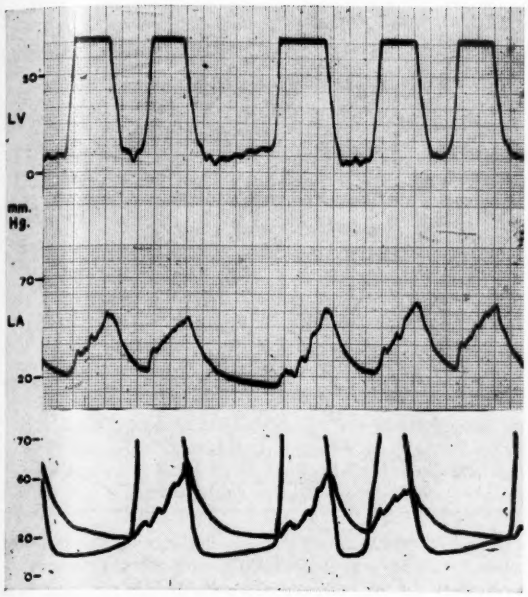

Fig. *1.* Direct measurement of the left atrial and left ventricular pressures in mitral stenosis and incompetence.

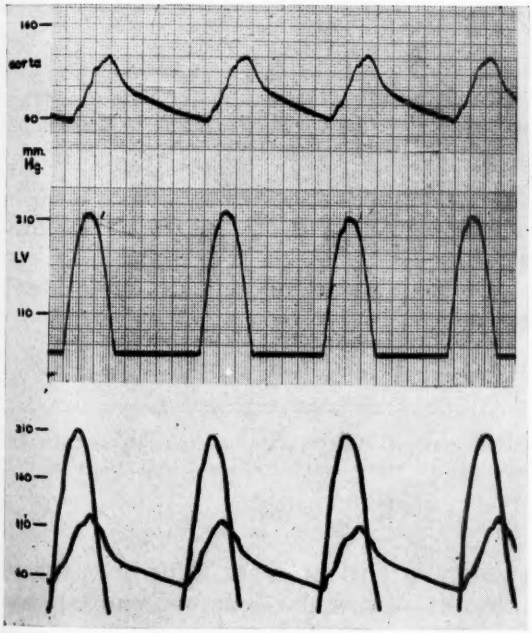

Fig. *2.* Direct measurement of the aortic and left ventricular pressures in aortic stenosis.

assumption that no regurgitation was present. Cardiac output, valvular areas, and pulmonary vascular resistance were expressed in relation to body surface area so as to minimize the effects of differences in body size. The Ry/v ratio[13] was calculated from the left atrial pressure pulse adjusted to a base line at the level of the sternal angle. Measurements of the aortic tidal peak time were corrected for variations in heart rate by dividing by the square root of the cycle length in seconds. The frontal area of the left atrium was measured with a planimeter on overpenetrating posterior-anterior radiographs taken at standard distance.

Results

A. Mitral stenosis (*Table I*). Sixty-nine patients with predominant mitral stenosis were studied. Some had soft basal murmurs, but there was no other evidence of aortic valvular disease. Thirteen additional patients had aortic valvular lesions of considerable degree. There was clinical evidence of slight or moderate mitral insufficiency in two thirds of the patients.

Measurements of left heart pressure were necessary in half of the patients with pulmonary vascular disease or with lesions of "critical" severity, i.e., cases in which there was doubt as to the need for operation. On the other hand, studies of the left heart were rarely required for the assessment of severe uncomplicated mitral stenosis or in patients with trivial disease, e.g., after successful commissurotomy. The left ventricu-

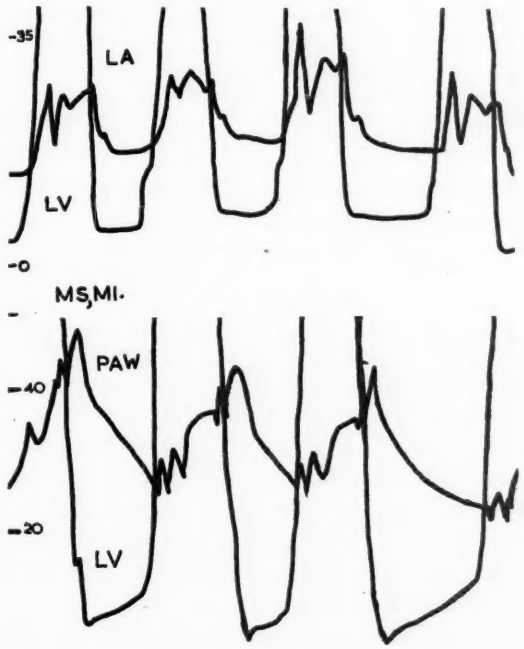

Fig. *3.* Superimposed left atrial (*above*) or pulmonary arterial wedged (*below*) and left ventricular diastolic pressures in two patients with combined mitral stenosis and incompetence.

Table I. *Eighty-two patients with predominant mitral stenosis**

	Total number	*Number with MI*	*Left heart pressure measured*		*Calculated mitral valvular area (cm.²/M.²)*	*LV mean diastolic pressure (mm. Hg)*	*Ry/v*		*Cardiac index (L./min./M.²)*
			LA	*LV*			*Pure MS*	*MS with MI*	
PVR more than 10 units per sq. meter	9	3	3	3	0.3	13	1.5	1.9	1.8
PVR 5 to 10 units per sq. meter	14	11	7	8	0.5	11	0.9	1.1	2.0
Severe uncomplicated MS	8	0	0	1	0.5	10	—	—	2.6
Severe MS with MI	10	10	3	8	0.4	9	—	1.7	2.3
MS of critical severity	14	8	4	7	0.8	9	0.9	1.7	2.6
MS with aortic valvular disease	13	5	3	12	0.9	11	1.1	—	2.6
Trivial MS	14	9	1	2	1.1	11	—	1.0	3.0

*For detailed analysis these patients are divided into seven groups, ranging from severe to trivial stenosis. Patients with an increased pulmonary vascular resistance (PVR) form the first two groups. Cases of severe mitral stenosis (MS) with mitral incompetence (MI) are separated from the uncomplicated cases for comparative purposes. In the patients with considerable aortic valvular disease the mitral stenosis was only moderately severe. Areas of the mitral valves were calculated from the hemodynamic data,[12] on the assumption that no regurgitation was present. Valvular areas, pulmonary vascular resistance, and cardiac output are expressed in terms of body surface area (per square meter). Ry/v ratio[13] was measured from left atrial pressure records.

Table II. *Twenty-five patients with predominant mitral incompetence**

	Total number	*Left heart pressure measured*		*LV mean diastolic pressure (mm. Hg)*	*Ry/v*	*Cardiac index (L./min./M.²)*
		LA	*LV*			
PVR more than 5 units per sq. meter	4	3	3	18	6	2.1
Severe uncomplicated MI	4	2	3	11	6	1.9
MI of critical severity	4	3	3	10	5	2.8
Trivial MI	8	1	1	16	—	2.9
MI with significant AI	5	0	5	13	—	2.7

*These patients are divided into five groups, ranging from severe to trivial incompetence. Patients with an increased pulmonary vascular resistance (PVR) form the first group. The last group in the table consists of patients with both aortic (AI) and mitral (MI) incompetence.

lar mean diastolic pressure was measured in 29 patients without aortic valvular disease and averaged 10 mm. Hg (range, 4 to 16 mm. Hg). In the patients with serious aortic valvular disease the mitral stenosis was only moderately severe. Measurements of left ventricular pressure were obtained in these cases primarily for evaluation of the aortic lesion.

B. Mitral incompetence (*Table II*). Twenty-five patients with predominant mitral insufficiency were studied. In 5 there was also significant aortic incompetence. The lesion was regarded as of "critical" severity in patients with signs of considerable left ventricular enlargement but few symptoms; the cardiac output was normal in this group. Measurements of pressure in the left heart were obtained in three quarters of the patients with severe mitral incompetence, but in only one quarter of those judged, on the basis of absence of left ventricular hypertrophy, to have trivial lesions. The left ventricular mean diastolic pressure was measured in 10 patients with isolated mitral insufficiency. In the uncomplicated cases the average value was 11 mm. Hg (range, 6 to 16 mm. Hg).

Table III. *Left atrial pressure pulse in 30 patients with mitral valvular disease**

	Pure MS	*MS and MI*	*Pure MI*
Number of cases	7	14	9
Cardiac index (L./min./M.²)	2.1	2.1	2.4
Frontal LA area (cm.²)	66	79	71
LA pulse pressure (v–y) (mm. Hg)	12	14	27
Ry/v ratio	1.2	1.7	5.6

*The average findings in the left atrial (LA) pressure pulse are compared in patients with pure mitral stenosis, mitral stenosis complicated by mild or moderate incompetence (MS + MI), and pure mitral incompetence.

Records of left atrial pressure were available in 30 patients with mitral valvular disease (Table III). The size of the left atrium, as judged from the posteroanterior radiograph, and the cardiac index were similar in patients with stenotic, incompetent, and combined lesions. High Ry/v ratios were found only in the group with pure mitral incompetence.

C. Aortic valvular disease (*Table IV*). Twenty-six patients with isolated aortic valvular disease, and 18 patients with combinations of aortic and mitral lesions were studied. The severity of the aortic stenosis varied greatly. Four patients had minor lesions, and in 5 more, classed as "critical," there was doubt as to the need for operation.

Left ventricular pressures were obtained in all but 2 of the patients with aortic valvular disease. The left ventricular mean diastolic pressure ranged from 5 to 35 mm. Hg. Measurements of aortic pressure were available in all cases. There was a tendency to a slower upstroke in patients with left ventricular failure, and a more rapid upstroke in those with mild lesions. The timing of the aortic tidal peak could not be related to the severity of the stenosis.

Discussion

Measurement of the diastolic pressure gradient across the mitral valve requires estimation of both left atrial and left ventricular pressures. It is generally agreed that the mean pulmonary arterial wedged pressure is a good index of the mean left atrial pressure, but the wave form may be considerably damped in transmission to the wedged catheter.[14] However, the simplicity of the wedged technique and the small risk entailed make it preferable when the information it gives is adequate. The error produced by using the mean wedged pressure as an estimate of left atrial pressure is small when the gradient is large (Fig. 3, *below*).

The mean left ventricular diastolic pressure in mitral stenosis averaged 10 mm. Hg

Table IV. *Forty-four patients with aortic valvular disease**

	Total number	*Calculated aortic valvular area (cm.²/M.²)*	*LV mean diastolic pressure (mm. Hg)*	*Cardiac index (L./min./M.²)*	*Aortic pulse*	
					Maximum upstroke (mm. Hg/sec.)	*Corrected tidal peak (sec.)*
AS with LV failure	4	0.25	28	2.3	380	0.29
Severe uncomplicated AS	9	0.3	11	2.3	770	0.24
Severe AS with AI	4	0.4	22	2.6	630	0.28
AS of critical severity	5	0.5	12	3.1	570	0.25
Mild uncomplicated AS	4	0.7	13	3.4	950	0.28
Severe AS with MS	4	0.3	9	2.1	570	0.27
Severe AS with AI and MS	5	0.4	13	2.7	1,100	0.24
Severe AI and MS or MI	9	—	11	2.8	1,470	0.19

*These patients are divided into five groups of isolated aortic valvular disease, ranging from severe to mild stenosis, and three groups of combined aortic and mitral valvular lesions. Patients in the first group had left ventricular failure at the time of study. The other patients with severe aortic stenosis are divided into two groups so that cases of uncomplicated stenosis may be compared with cases in which there was associated aortic incompetence. Aortic valvular area was calculated from the hemodynamic data,[12] on the assumption that no regurgitation was present, and is expressed in terms of body surface area (per square meter).

in this study, with considerable individual variation, and similar findings have been reported by others.[15] The use of an arbitrary value of 5 mm. Hg[12] will lead to considerable error in the calculation of the mitral valvular area if the gradient is small. If the wedged pressure is high and there is no associated abnormality which might raise the left ventricular diastolic pressure, such as aortic valvular disease or mitral incompetence, a value for the left ventricular diastolic pressure may be assumed without serious error. If the cardiac output is normal, a low wedged pressure indicates a mild lesion. In other circumstances, for instance, moderate elevation of the wedged pressure, evidence of left ventricular disease, or a low wedged pressure with restriction of the cardiac output, left ventricular pressures are needed for accurate assessment of the stenosis. Left atrial pressures are required only if a small gradient must be measured precisely because the cardiac output is low, as in patients with pulmonary vascular obstruction or tricuspid valvular disease.

In predominant mitral incompetence the left atrial pressure may appear to show diastasis when, in fact, a considerable gradient persists (Fig. 3, *above*). Measurement of left ventricular pressure is probably necessary unless the wedged pressure falls to normal levels at the end of diastole. Left atrial puncture is needed to measure a small gradient accurately, but is rarely of practical value because a small gradient may be found in mitral incompetence without significant stenosis.[17]

The left atrial v wave in mitral valvular disease is related to the regurgitant flow, but is also influenced by the systolic inflow from the pulmonary veins and by the volume and mechanical properties of the left atrium.[16] The Ry/v ratio has the advantage of taking into consideration the increasing rigidity of the left atrial wall as the chamber is distended.[13] However, the effects of mitral regurgitation on the left atrial pressure pulse cannot be distinguished with certainty if a mitral gradient persists throughout diastole.[16] Variations in left atrial volume and cardiac output are relatively small (Table III), and it seems likely that differences in the elasticity of the left atrial wall are mainly responsible for this difficulty.

The character of ventricular ejection and the effects of aortic regurgitation determine the form of the aortic pressure pulse, but the physical properties of the aorta and the timing of flow to the peripheral vessels[18] also play a part. The separation of these factors is difficult, and in the present study the maximum rate of rise in pressure and the corrected tidal peak time did not distinguish aortic stenosis from stenosis with moderate insufficiency. A prominent anacrotic wave in aortic stenosis may produce a rapid upstroke, and a large stroke volume may lead to a sustained pulse with only a moderate degree of stenosis. Left ventricular and aortic pressures (Fig. 2) are needed to estimate the severity of aortic stenosis accurately, but the use of peripheral arterial pressures produces little error if the gradient is large.

Conclusions

Measurements of left ventricular pressure are necessary for the precise assessment of mitral valvular disease when there are lesions producing left ventricular hypertrophy or restricting the cardiac output, or when the pulmonary arterial wedged pressure is only moderately elevated. When the difference between mean wedged and left ventricular diastolic pressures is small, left atrial puncture is needed to measure the gradient accurately. Direct left atrial pressures are rarely of value in assessing mitral incompetence.

In aortic stenosis, left ventricular pressures are needed if there is doubt as to the severity of the obstruction.

Summary

The indications for direct measurement of left atrial and left ventricular pressure are analyzed in the light of experience with 133 cases of mitral or aortic valvular disease. Left ventricular pressures are more often needed than direct left atrial pressures because the pulmonary arterial wedged pressure frequently gives adequate information without the risks of left atrial puncture.

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Pulmonary venoarterial shunting in hepatic cirrhosis

Including a case with cirsoid aneurysm of the thoracic wall

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The association of peripheral cyanosis, clubbing of the digits, and liver disease was first recognized in 1884, by Fluckiger.[1] Gilbert and Fourier[2] made similar observations in children with this disease in the absence of overt pulmonary disease. Keys and Snell[3] ascribed the cause of the arterial desaturation in patients with cirrhosis of the liver to a shift of the oxyhemoglobin dissociation curve to the right. Subsequently, Wilson and coworkers[4] demonstrated the existence of a moderate degree of pulmonary venoarterial admixture in their 10 patients with cirrhosis of the liver.

Cutaneous vascular lesions are commonly observed in patients with cirrhosis of the liver.[5] The cause of such lesions is unknown, but they have tentatively been attributed to an elevated level of circulating estrogen and not to arterial desaturation. Thus, the mechanism of reduced arterial oxygen saturation in patients with cirrhosis of the liver remains partially unclear, as does the possible relation of this change to other vascular disturbances noted in this disease.

The purpose of this study was to examine alveolar-arterial gas exchange so as to estimate the degree of venoarterial admixture present in 15 patients with cirrhosis of the liver. The development of a cirsoid aneurysm of the thoracic wall in a 57-year-old man with Laennec's cirrhosis, who was studied over a period of several years, is reported in detail.

Materials and methods

Fifteen patients, 13 men and 2 women, with cirrhosis of the liver were studied while they were resting in the supine position, breathing, first, ambient air and, then, 100 per cent oxygen. The ages of these patients ranged between 16 and 63 years (average, 47.3 years). The duration of their illnesses ranged between 2 and 9 years. Twelve patients had Laennec's cirrhosis of the liver, 1 patient (Case 14) had juvenile cirrhosis, and in another patient (Case 12), cirrhosis was thought to be secondary to repeated exposure to various chemical toxins. In all, the diagnosis was made on clinical and laboratory grounds and verified either by needle biopsy of the liver or at autopsy.

Arterial oxygen and carbon-dioxide contents were determined by the method of Van Slyke and Neill. Expired oxygen and carbon-dioxide concentrations were determined by the Beckman E-2 and Liston-Becker analyzers, respectively. Arterial

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Table I. Gaseous exchange in patients with cirrhosis of the liver, on breathing room air

Case	*Arterial oxygen saturation (%)*	*Arterial oxygen tension (mm. Hg)*	*Arterial carbon-dioxide tension (mm. Hg)*	*Alveolar-arterial oxygen tension gradient (mm. Hg)*
1.	90	71	37	38
2.	94	78	36	34
3.	93	71	36	41
4.	94	78	38	25
5.	92	88	37	24
6.	81	65	41	45
7.	92	75	27	31
8.	93	79	28	32
9.	80	45	40	58
10.	89	59	36	46
11a.	86	52	29	63
11b.	94	61	31	41
12.	90	75	47	46
13a.	78	41	31	75
14.	89	60	32	56
15.	94	80	31	37
Range	78–94	41–88	27–47	24–75
Mean ± S.D.	89 ± 9.7	67 ± 13	34.8 ± 5.3	43 ± 16
Normal	94.9 ± 2.6	85.0 ± 13	39.0 ± 4.0	13.0 ± 6.5

blood pH was determined by the Beckman GS pH meter. The carbon-dioxide tension of the arterial blood was obtained from the Singer-Hastings nomogram, using the whole blood arterial carbon-dioxide content, and pH. The arterial oxygen tension (Pa_{O_2}) was determined polarographically from whole blood by a method[6] employing the Clark electrode.[7] The alveolar oxygen tension (PA_{O_2}) was calculated from the alveolar air equation. The difference between the alveolar oxygen tension and the arterial oxygen tension is the A-a gradient. Under the conditions of these experiments the A-a gradient in normal individuals when they are breathing room air is 13 ± 6.5 mm. of mercury.[8]

After the ambient-air studies were completed, the patients breathed pure oxygen for at least 30 minutes. This allows sufficient time to complete nitrogen washout from all alveolar spaces, resulting in virtually complete equilibrium between the alveolar air and pulmonary capillary blood. Under these circumstances, an alveolar-arterial (A-a) oxygen tension gradient of less than 60 mm. of mercury is observed in normal individuals in the supine position, thus indicating the presence of a small degree of venoarterial admixture even in normal subjects. A larger A-a oxygen tension gradient is diagnostic of abnormal pulmonary venoarterial admixture. The magnitude of this shunt can be estimated from the following equation[4,9]:

$$\% \text{ shunt} = 100\left(1 - \frac{AV_{O_2} \text{ diff.}}{AV_{O_2} \text{ diff.} + G}\right)$$

where G represents the A-a oxygen tension gradient multiplied by (0.003) the Sendroy solubility factor for oxygen at 37.5°C., expressed as milliliters per millimeter of mercury. Utilizing this equation and assuming an oxygen difference of 4.3 volumes per cent between the systemic and the pulmonary arteries, we estimated the fraction of the cardiac output represented by the venoarterial shunt in each patient. The assumption of an arterial mixed venous oxygen content difference of 4.3 volumes per cent is permissible because extreme variations in this factor make only small differences in the estimated shunt.

Results

When they were breathing room air, a majority of the patients had a moderate degree of arterial oxygen desaturation, as illustrated in Table I. The mean arterial oxygen saturation for the group was 89

Table II. *Pulmonary venoarterial admixture in patients with cirrhosis of the liver, using the 100 per cent oxygen breathing method*

Case	*Arterial oxygen tension* (Pa_{O_2}) *(mm. Hg)*	*Arterial carbon-dioxide tension* (Pa_{CO_2}) *(mm. Hg)*	*A-a oxygen tension gradient (mm. Hg)*	*% "Shunt"*
1.	191	37	462	24
2.	356	25	310	18
3.	608	39	60	4
4.	483	39	182	11
5.	506	38	155	10
6.	248	41	414	22
7.	593	24	64	4
8.	237	29	443	24
9.	210	37	436	24
10.	599	40	63	4
11a.	228	36	429	23
11b.	209	42	439	23
12.	448	50	212	13
13a.	199	31	467	25
13b.	201	31	465	24
14.	90	31	577	29
15.	293	30	376	21
Range	90–608	24–50	60–577	4–29
Mean ± S.D.	355 ± 168	35 ± 7	327 ± 168	18 ± 8

per cent, and ranged between 78 and 94 per cent. The mean alveolar-arterial (A-a) oxygen tension gradient was 43 mm. of mercury, and ranged between 24 and 75 mm. of mercury.

In Table II, blood gas findings on 100 per cent oxygen are reported. A large alveolar-arterial (A-a) oxygen tension gradient was found in 12 patients. The mean A-a oxygen tension gradient for the group was 327 mm. of mercury and corresponded to a mean venoarterial admixture of 18.0 per cent of the cardiac output. Two cases, Cases 11 and 13, were studied on two occasions separated by an interval of several months. The degree of venoarterial admixture estimated in the second study did not change from that obtained earlier. The mean venoarterial admixture will drop to 17 per cent of the cardiac output if these two values are excluded.

Case report

A 57-year-old-white man developed ascites and jaundice in July, 1948 (Case 13 in Tables I and II). He gave a history of excessive alcoholic intake for the previous 30 years. His ascites and jaundice gradually subsided after liver therapy and abstinence from alcohol. In April, 1950, hoarseness, exertional dyspnea, and cyanosis appeared. Numerous spider nevi were observed over the upper extremities and the thorax. The liver was moderately enlarged, firm, and nontender. The spleen was not felt. A vascular lump, "the size of a quarter of a dollar," appeared in the left lower posterior axillary region, and a systolic murmur was heard over it. There was no history of previous trauma to this site. In November of that year he experienced two episodes of hematemesis and melena. The bleeding was controlled with the application of a Blakemore tube. In 1951, he experienced frequent infections of the upper respiratory tract, and clubbing of the fingers and toes was observed for the first time. As the vascular lump enlarged, cyanosis and dyspnea progressively increased. A to-and-fro murmur was now heard over the mass. The heart had increased moderately in size. There was no evidence of ascites or peripheral edema. The tip of the spleen became palpable.

When last seen in February, 1954, the patient exhibited definite cyanosis of the face, lips, and nail beds. Clubbing of the fingers and toes was marked. The blood pressure was 126/70 mm. Hg. The neck veins were slightly distended. Fine crepitant râles were heard over both lung bases. Overlying the tenth rib, in the left axillary region, there was an irregular, nontender, partly compressible vascular mass that was roughly 13 cm. in diameter and was raised about 4 cm. above the chest wall. A group of distended veins was clearly visible at its upper end (Fig. 1). A to-and-fro murmur was heard over the mass. The heart size was enlarged and a Grade 2 apical systolic murmur was heard. The surface of the liver was not grossly nodular, and the

edge was felt 6 cm. below the costal margin. The spleen was palpable. The distribution of pubic hair was of a female type, and axillary hair was sparse. The testicles were atrophic. Bilateral gynecomastia was evident. There was a trace of pretibial edema.

The pertinent laboratory findings were the following: hemoglobin 16.8-17.5 Gm. per 100 ml.; hemotocrit 46-48 per cent; normal total leukocyte and differential counts; normal urinalysis; serum proteins 4.9 Gm. per cent (albumin 1.7 Gm. per cent); cephalin flocculation 4+; thymol turbidity 2.0-6.3 units; Bromosulphalein retention 35-41 per cent in 45 minutes; total serum bilirubin 1.6 mg. per cent (direct, 1.1 mg. per cent); total serum cholesterol 182 mg. per cent (its ester, 98 mg. per cent); alkaline phosphatase 8.9 Bodansky units. The 2-hour urine urobilinogen level varied between 3.3 and 6.6 Ehrlich units. The blood urea nitrogen and serum electrolytes were within normal limits.

The electrocardiogram revealed nonspecific S-T and T-wave changes. Cardiac fluoroscopy demonstrated a diffuse cardiomegaly. The pulmonary arteries were actively pulsating; otherwise, the pulmonary vasculature was normal. Injection of radiopaque material into the vascular mass revealed the flow of the dye into vascular structures which were mainly below the diaphragm (Fig. 2). A number of physiologic studies were performed; these included pulmonary function tests (Table III), measurements of the oxygen contents of blood withdrawn simultaneously from the brachial artery and the aneurysmal mass, and cardiac catheterization (Tables IV and V).

At postmortem (performed at another hospital) the large left thoracic wall mass measured 15 by 10 by 4 cm. It was composed of dilated vessels, subcutaneous tissue, and muscle. The vessels appeared to be mainly tortuous elongated veins arising from the intercostal veins. There was no obvious arteriovenous communication within the mass (postmortem injection study was not performed). The vascular mass extended from the subcutaneous area to the subpleural space. The pleural space between the vascular mass and the left lung was obliterated by firm fibrous adhesions. In it, no vessel of significant caliber was observed.

The lungs weighed 1,900 grams each. The pulmonary artery showed no atheromatous plaques, and no gross evidence of arteriovenous communications was observed in the lungs (injection studies were not done). The pleural spaces were free of adhesions, with the exception of the area adjacent to the thoracic mass. The heart weighed 480 grams and demonstrated no valvular lesion. The thickness of the left ventricular wall at the apex was 1.0 cm.; that of the right ventricle was 0.2-0.3 cm. The myocardium was flabby and of a reddish-brown color. The right ventricular endocardium was thicker than noted elsewhere. The coronary arteries were patent.

The liver weighed 1,150 grams. Its surface was finely nodular; the diameters of these nodules ranged from 2 to 5 mm. Similarly, the cut surface demonstrated the same nodularity, altering the normal liver architecture. Each pseudolobule was surrounded by a fairly uniform zone of fibrous tissue.

Table III. *Pulmonary function studies in Case 13*

	December, 1951	*January, 1954*	*Predicted value*
Respiratory rate (per min.)	16	20	—
Tidal volume (ml.)	866	680	—
Resting ventilation (L./min.)	13.9	13.6	—
Inspiratory capacity (L.)	4.0	3.57	—
Vital capacity (L.)	4.5 (112%*)	4.49 (112%*)	4.0
Forced expiratory volume, 3 sec. (L.)	3.75 (89%*)	3.57 (84%*)	4.25
Maximum breathing capacity (L.)	110 (88%*)	115 (92%*)	125
Functional respiratory volume (ml.)	—	3,144	—
Expiratory reserve (ml.)	—	1,350	—
Residual volume (ml.)	—	1,794	1,575
Total lung capacity (ml.)	—	6,714	5,555
$\frac{RV}{TC} \times 100$	—	26.7	<28
7-minute nitrogen elimination, index of intrapulmonary gas distribution (%)	—	3.4	<2.5
Oxygen consumption (ml.)	235	221	—
Oxygen removal rate (ml./L.)	17	16.4	—
Arterial oxygen saturation (%)			
Room air: Rest	75	69	>96
Exercise	65	62	—
100% oxygen: Rest	100	100	100
Exercise	85	83	100

*Represents the per cent of predicted normal value.

Table IV. *Per cent oxygen saturation of the blood samples withdrawn simultaneously from the brachial artery and the aneurysmal mass*

Date	*Brachial artery*	*Aneurysmal mass*
May, 1950	81	81
December, 1951	75	56
January, 1954	69	73
February, 1954	63	65

An increased number of bile ducts was noted. The spleen weighed 300 grams. It possessed a thick capsule and demonstrated the features of chronic passive congestion. In the lower esophagus, many large, thick-walled veins were present in the submucosa, and a number of them extended to within several micra from the lumen of the esophagus. Numerous dilated vessels were present in the muscularis layer and in the surrounding tissue of the esophagus.

Discussion

Arterial desaturation in patients with cirrhosis of the liver may result from either a decreased affinity of hemoglobin for oxygen[3] or from altered exchange of pulmonary gases. As to the former cause, Rodman and co-workers[10] were unable to demonstrate any displacement of the oxyhemoglobin dissociation curve in their cirrhotic patients, suggesting that the hemoglobin affinity for oxygen in a cirrhotic patient is normal. With regard to the alternate cause, cirrhotic patients have an increased tendency to develop frequent respiratory infections, which may result in permanent changes in the lung tissue (fibrosis and thickened alveolar membrane) and a decrease in effective oxygen exchange. Pulmonary venoarterial admixture occurs in the presence of perfused but hypoventilated lung spaces. It is reasonable to assume that ascites could have contributed to alterations in the relationships between ventilation and blood flow. Such a state may be completely corrected by the breathing of pure oxygen, which results in virtually complete equilibrium between the alveolar and arterial oxygen tensions,[11] unless the venous admixture is due to a direct venoarterial communication in the lungs.

A large A-a gradient was demonstrated in 12 of these 15 patients after they had breathed pure oxygen for at least 30 minutes (Table II). These gradients corresponded to venoarterial shunts ranging from 10 to 29 per cent of the respective cardiac outputs. The pulmonary venoarterial shunting for the whole group averaged 18 per cent. Although the degree of pulmonary shunting found in the patients of this study is similar to that found by Rodman and co-workers,[12] it is greater than that reported previously by others.[4,13-15] This discrepancy in the reported magnitude of the pulmonary admixture may be due to the severity and the duration of the liver disease, and in part to the methods used in the respective studies. In the 3 patients (Cases 3, 7, 10) who had normal A-a gradients when breathing 100 per cent oxygen, the observed hypoxemia when they were breathing room air must have been caused by one or more of the other factors discussed

Table V. *Findings at cardiac catheterization—Case 13*

	Pressures (S/D) (mm. Hg)	*Oxygen content (vol. %)*	*Oxygen saturation (%)*	*Dye curve**	
				AT (sec.)	*PT (sec.)*
Pulmonary artery	24/11	11.98	64	6	11
Aneurysmal mass	44/33	14.59	73	11	16
Brachial artery	125/66	13.83	69		

Cardiac output 9.2 L./min.
Cardiac index 4.9 L./min./M.^{2}

*T-1824 dye curve recorded by the ear-oximeter. AT: Appearance time. PT: Peak time.

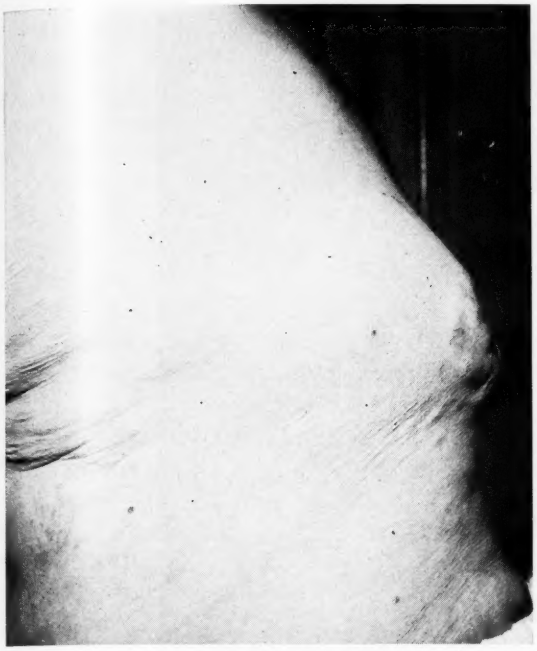

Fig. *1.* Photograph of the vascular mass in the left thoracic wall.

above. Cases 3 and 10 had large ascites, and Case 7 had a moderate collection of abdominal fluid.

Two possible sites of venoarterial admixture in human beings with cirrhosis of the liver have been anatomically described. Calabresi and Abelmann[16] demonstrated, by colored plastic solution injected into the portal veins, direct venous communications between the periesophageal veins and the pulmonary veins at postmortem in only 2 of their patients with cirrhosis of the liver. They postulated that venous admixture occurred through these channels. The actual magnitude of such shunts would necessarily be greater than those which we estimated, since the portal venous blood has a higher oxygen content than the mixed venous blood of the pulmonary artery.[17] Portal hypertension was presumed to be responsible for the development of shunting of venous blood from the portal to the pulmonary veins. In Case 15, an estimated 21 per cent shunt was observed even after the portal vein was surgically anastomosed to the inferior vena cava, with alleviation of the portal hypertension, thus suggesting that the shunting measured is not directly related to portal hypertension.

A second possible site of venoarterial admixture is direct noncapillary communications of small pulmonary arteries with pulmonary veins, as described by Rydell and Hoffbauer[18] and by Hales[19] and by Murray and co-workers[20] in juvenile and postnecrotic cirrhosis. Normally, in human beings as well as in animals, arteriovenous anastomoses larger than capillaries exist in the lungs.[21-23] Such anastomoses are known to be located beneath the visceral pleura and in the peribronchial area. They can become functional under the impact of various stimuli.[24,25]

These channels could conceivably open in the presence of a circulating vasodilator. Such a substance might well originate in the cirrhotic liver or in the intestinal tract (as a metabolite) and can be shunted through the liver, activating the pulmonary arteriovenous anastomosis. The chemical nature of this vasodilator material has not yet been described. A vasodepressor material (VDM, or reduced ferritin) has been described by Shorr and co-workers[26] to be formed in the liver in the presence of hypoxia; it is conceivable that the cirrhotic liver produces this material because of its reduced blood flow.[27] The flavonoid rutin, a specific antagonist of reduced ferritin,[28] reverted the peripheral circulatory changes in patients with clubbed digits to normal, suggesting at least that in the cirrhotic patients with clubbing, VDM may be present in the systemic circulation.[29]

The association of a vascular mass (hemangioma or cirsoid aneurysm) and cirrhosis of the liver was briefly reported previously in 2 patients with severe liver disease; in one, the vascular mass was located near the top of a buttock.[5] The vascular mass in our patient occurred spontaneously without known previous trauma. It was considered to represent a collection of arteriovenous channels of the intercostal vessels, since its luminal pressure was intermediate between that of the brachial and the pulmonary arteries (Table V). This mass emptied mainly into venous channels below the diaphragm, as was demonstrated radiographically by the flow of the radiopaque material injected into its lumen—and also by the delayed systemic appearance of Evans blue dye

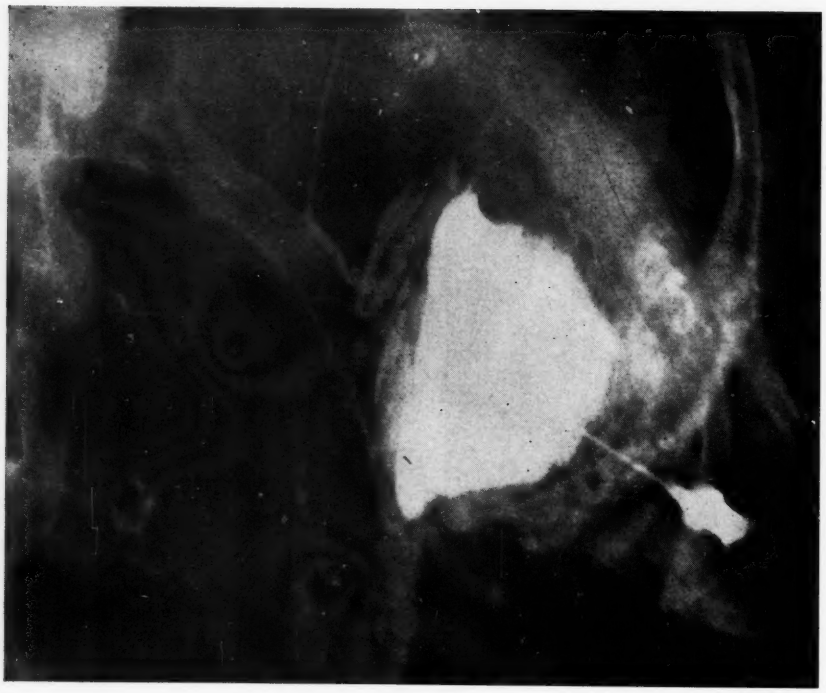

Fig. *2*. X-ray film of the radiopaque material injected into the thoracic vascular mass, demonstrating its size and the flow of this material to neighboring vessels.

injected into its lumen, as compared to an early appearance of the dye when it was injected into the pulmonary artery (Table V).

The oxygen saturation of the blood from the aneurysmal mass was essentially the same as that of a simultaneously drawn sample of arterial blood (Table IV). The comparatively high oxygen content of the sample of blood from the mass in 1954, along with pressure measurements, suggested the presence of arterial connections, with observed differences representing phasic variations in arterial saturation between the two sites. On one occasion the oxygen saturation of the blood obtained from the mass was lower than that found in the arterial blood, suggesting that, fortuitously, systemic venous blood was obtained. No pressure recording was made on that occasion.

Historically, the appearance of a small, painless, nontender mass in the left thoracic wall, and its subsequent development to a larger mass, suggested to us the presence of a circulating vasodilator material capable of enlarging nonpatent arteriovenous communications. In patients with cirrhosis, clubbing of the fingers and palmar erythema are associated with small arteriovenous oxygen and carbon-dioxide differences across the hands, suggestive of peripheral shunting, presumably through the existing arteriovenous anastomosis in the hands.[9] It is postulated that this peripheral shunting was the result of an active circulating vasodilator.

Clinically, the findings of clubbing of the digits, cyanosis, secondary polycythemia, normal pulmonary function, and actively pulsating pulmonary arteries suggested the presence of pulmonary arteriovenous fistulae. The marked drop in the oxygen saturation of the arterial blood to 83 per cent and 85 per cent on two separate occasions (Table III) on moderate exercise during the breathing of 100 per cent oxygen is also characteristic of central venoarterial admixture. The portion of the cardiac output that was shunted at rest amounted to 24 to 25 per cent. Dye-injection studies during right heart catheterization excluded intracardiac shunts; this was confirmed on postmortem examination. Therefore, it seems most likely that this is an example of intrapulmonary shunting. Unfortunately,

no attempt was made at postmortem examination to demonstrate anatomically the existence of arteriovenous anastomoses or to localize the site of shunting by injection studies.

It is possible that two sites of pulmonary venoarterial shunting may be operating simultaneously, or one may predominate in cirrhosis of the liver. The persistence of hypoxia and a large venoarterial shunt after portacaval anastomosis, and the increased shunting in the reported case after exercise, favor the hypothesis that venoarterial admixture is caused by direct communications of small pulmonary arteries and veins. Using isotope-labeled krypton (Kr^{85}), Fritts and co-workers[15] similarly observed that shunting occurred at both sites, and found that the major fraction of the venoarterial admixture occurred between the portal and the pulmonary veins. But they pointed out that oxygen and krypton gas behave differently and suggested that these two methods probably detect different anatomic pathways. Further investigation is needed to elucidate the location and nature of these shunts.

Conclusions

A moderate degree of systemic arterial desaturation and an elevated alveolar-arterial oxygen tension gradient were found in 12 of 15 patients with cirrhosis of the liver. This was considered to be the result of venoarterial admixture. The magnitude of the shunt averaged 18 per cent of the cardiac output. Direct communications between the small pulmonary arteries and veins represent most likely a major cause of shunting.

An adult patient with alcoholic cirrhosis of the liver and a cirsoid aneurysm of the thoracic wall was described. The sudden appearance of the thoracic aneurysmal mass in the absence of trauma, and its subsequent development, suggests the possibility that such lesions may be due to the presence of a circulating vasodilator substance.

The clinical and laboratory findings of clubbed fingers, polycythemia, arterial desaturation, and postexercise increase in the degree of pulmonary venoarterial admixture suggested the presence of pulmonary arteriovenous fistulae.

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Experimental and laboratory reports

The technique of estimating the instantaneous aortic blood velocity in man from the pressure gradient

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The time relationships between pressure and blood velocity in the ascending aorta can be used to define the mechanical function of the heart. To the extent that the mechanical function is altered early in disease, evaluation of these pressure-velocity relationships has important clinical as well as biophysical implications.

It is possible to estimate both the aortic pressure and the instantaneous blood velocity by the use of a catheter method.[1] This method requires accurate measurement of the instantaneous lateral pressures at two relatively close points along the axis of the aorta. The difference between these pressures is an approximate measure of the instantaneous pressure gradient from which the blood velocity may be computed by means of simple analog computer methods.

The computation of the aortic blood velocity from the spatial pressure gradient requires extremely accurate measurement of the pressure and meticulous attention to a number of experimental details. A number of problems are raised by these requirements in the application of this technique to studies in human subjects. It is the purpose of this report to present certain approaches to many of these problems and to make available the details necessary to apply this method successfully in the clinical physiology laboratory. Examples are also given which illustrate the pressure-velocity relationships as measured in patients with nonvalvular myocardial disease and after the administration of certain pharmacologic agents.

The discussion of the application of the computed pressure gradient technique may be divided into five general areas: catheter, gauges, electrical circuits and amplifiers, calibration, and evaluation of the total system response.

Catheter. The catheter, as diagrammatically illustrated in Fig. 1, is of a special double-lumen design,† with two lateral pressure taps at the end of each lumen. The entry to each lumen is separated by a distance of 5 cm. The No. 6½ French catheter will pass through a short beveled modification of a No. 12 gauge Robb needle. The stopcocks connecting the catheter to the gauges must be made to fine tolerance.‡

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‡Many standard American stopcocks have proved to be unsatisfactory in this regard. Satisfactory performance has been uniformly obtained with the No. 12-T three-way stopcocks obtained from Ole Dich, 18 Holmevej, Brondby Strand, Hvidovre, Denmark; or with the EMT 473 stopcock of the Elema-Schonander AB, Stockholm-Solna, Sweden.

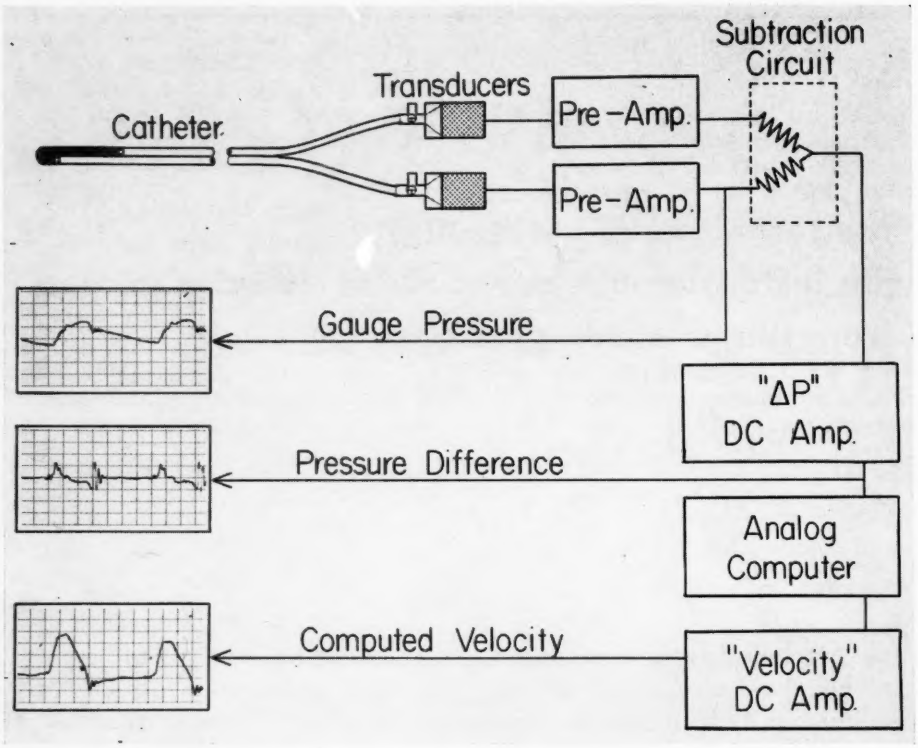

Fig. *1*. A diagrammatic representation of the system used to assess instantaneous blood velocity in man. The methods of application of the component parts are discussed in the text.

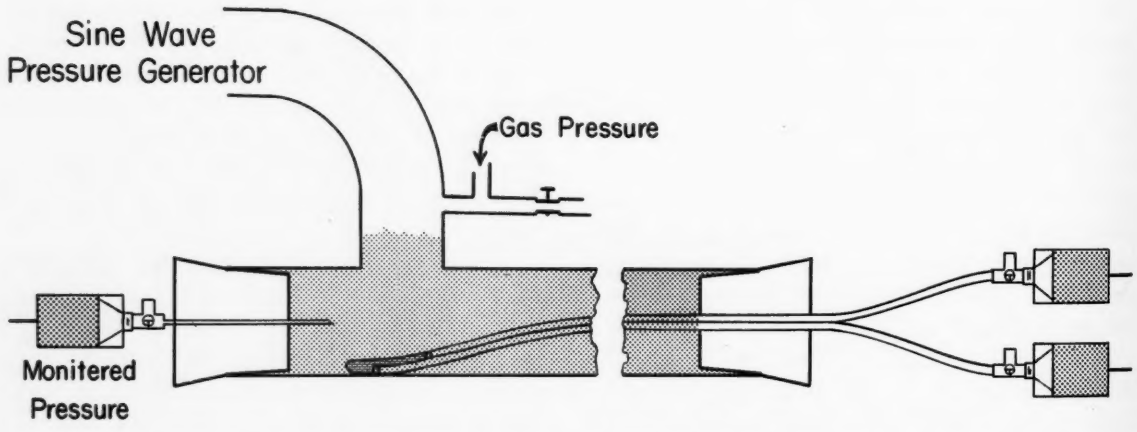

Fig. *2*. The system used to evaluate the static and dynamic response of the catheter-gauge system under sterile conditions.

Gauges. The gauges used are Statham P-23Db gauges. We have used two other types of differential pressure gauges but have not found their performance characteristics as satisfactory as the two-gauge Statham system. In order to obtain a differential pressure from two gauges, it is useful to reverse the polarity of one of the gauges, and then electrically sum the two signals. This is easily performed by reversing the leads of either the excitation circuit or the signal circuit on the gauge which is connected to the downstream orifices.

Amplifiers and electrical circuits. Each gauge is connected to a carrier preamplifier. We have used the Series 450 Sanborn preamplifier, although any amplifier would

suffice that has extreme accuracy of setting and minimal base-line and gain drift. As illustrated in Fig. 1, the single-ended outputs of each amplifier are connected to a subtraction circuit. The voltage output of this subtraction circuit is then amplified by a DC amplifier (the "Δ P" DC amplifier in Fig. 1) having fine control of the zero position and having minimal drift, since any base-line shift will be magnified by the subsequent computation.

The instantaneous aortic blood velocity is continuously computed from the instantaneous pressure difference by an analog device which is either a passive network or preferably one including an operational amplifier.[2] In order to record the computed velocity adequately, further amplification may be necessary (the "Velocity" DC amplifier in Fig. 1).

The single-ended gauge pressure, the pressure difference, and the computed velocity can be recorded as illustrated in Fig. 1. A direct-writing recorder has advantages since it is desirable to monitor immediately the pressure difference and computed velocity.

The problems encountered in setting up the amplifiers are threefold: (1) adjustment of the gains of the carrier preamplifiers so that the output voltage will always be in the linear range, (2) setting of the gains of the carrier preamplifiers to exactly equal each other, (3) fixation of the zero position so that when zero pressure is applied to both lumens, the voltage output of the subtraction circuit is zero.

Calibration. The method of calibrating the system involves the application of a known constant pressure difference to permit a measure of the initial slope of the computed velocity versus time curve. The simplest way to apply a steady signal difference is to use the calibration button of one of the pressure amplifiers to obtain a constant voltage which can be calibrated as an equivalent constant pressure. The calibration factor, k, in units of centimeters

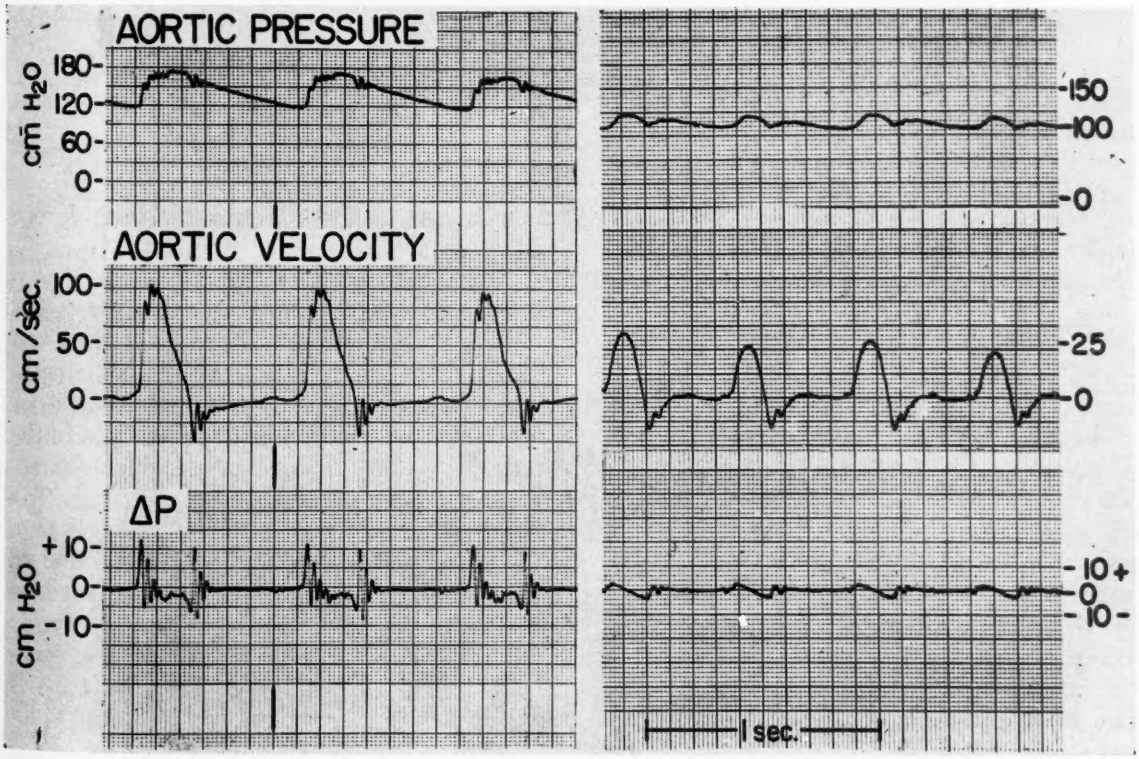

Fig. 3. On the left, from the top down, are the central aortic pressure, computed aortic blood velocity, and measured spatial pressure difference of a presumably normal 46-year-old man (C. H. 02-83-44). On the right are the same data for a 32-year-old man (R.F. 02-80-97) with severe myocardial insufficiency and mechanical pulsus alternans. Note that the calibration scales on the two records are different for the computed velocity and pressure difference.

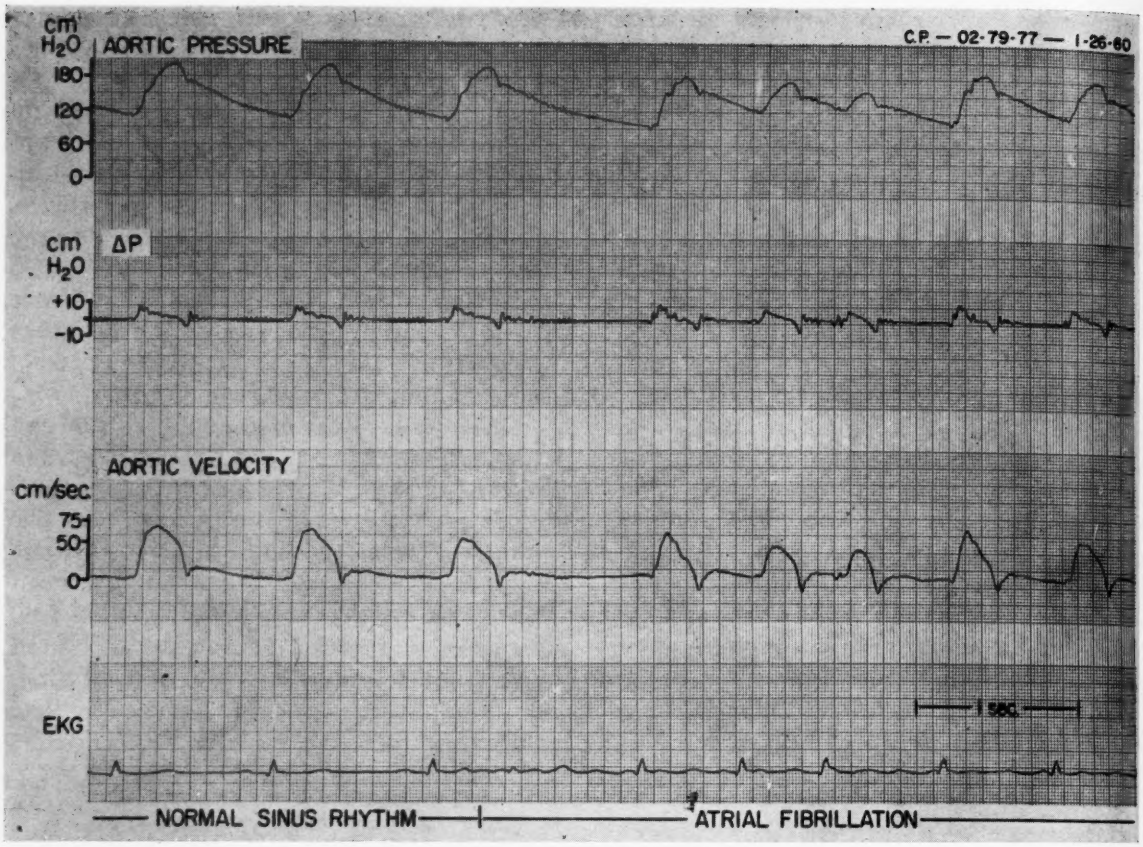

Fig. 4. A record of central aortic pressure, measured pressure difference, computed velocity, and electrocardiogram of a 46-year-old man with known myocardial fibrosis, during spontaneous change from normal sinus rhythm to atrial fibrillation.

per second of velocity per millimeter of deflection on the record is then obtained from the following:

$$k = \frac{P_e \cdot g}{\rho \cdot \Delta x \cdot S}$$

where P_e is the equivalent pressure of the calibration signal in centimeters of H_2O (Gm./cm.^{2}); ρ is the density of blood (1.05 Gm./cm.^{3}); Δx is the catheter pressure tap separation (centimeters); g is the gravitational constant (980 cm./sec.^{2}); and S is the initial slope of the computed velocity on the record (millimeters of deflection on the record per second).

Evaluation of catheter-gauge response. The main problem encountered with this system is the removal of all gas bubbles from the catheter-stopcock-gauge system so that optimal performance characteristics can be achieved. A good method for removing minute bubbles is to let a slow drip of sterile saline containing about 0.5 per cent of alcohol flow through each lumen for several hours.

The application of the computed pressure gradient technique to man requires that strict sterile procedure be maintained throughout. After sterilization of the catheter-gauge system,* and immediately prior to the procedure, a careful evaluation of the static and dynamic performance characteristics of the system is carried out. The use of a long glass cylinder with a side arm, as illustrated in Fig. 2, has been found to be convenient. The sterile catheter is placed in the previously sterilized tube. A sterile split rubber plug is used to close the opening around the catheter, and the tube is filled with 0.2 per cent benzalkonium chloride. Steady pressure can be applied to the system from a constant-flow, high-pressure source of gas through a connecting tube having a "bleeder" side arm which permits

*Sterilization of the catheter in this laboratory is performed with ethylene oxide gas.

the pressure to be adjusted to the desired level.

The static response is evaluated by the application of a steady pressure to both lumens of the catheter simultaneously and the adjusting of the gain control on one of the carrier amplifiers so that the pressure difference indicated between the gauges remains near zero throughout the range of study. An error of less than 0.3 per cent over the physiologic range can usually be achieved. An error greater than this may introduce appreciable distortion in the measured pressure difference. After both amplifier-gauge systems are adjusted to have the same gain, this gain is then calibrated against a water manometer by the application of a known pressure to one gauge while the other is held at a constant reference pressure.

The dynamic response of the system is evaluated by applying a sinusoidal pressure to the air column in the upright side arm of the tube as illustrated in Fig. 2. This sinusoidal pressure is imposed upon the constant base-line pressure and is produced by a modified model airplane engine piston which is driven by a variable-speed motor. The pressure in the fluid near the tip of the catheter is directly measured for comparative purposes by a separate gauge-trocar system that is dynamically accurate through 40 c.p.s. At the present time, we believe that each side of the catheter should have less than a ± 5 per cent amplitude error and no appreciable phase dis-

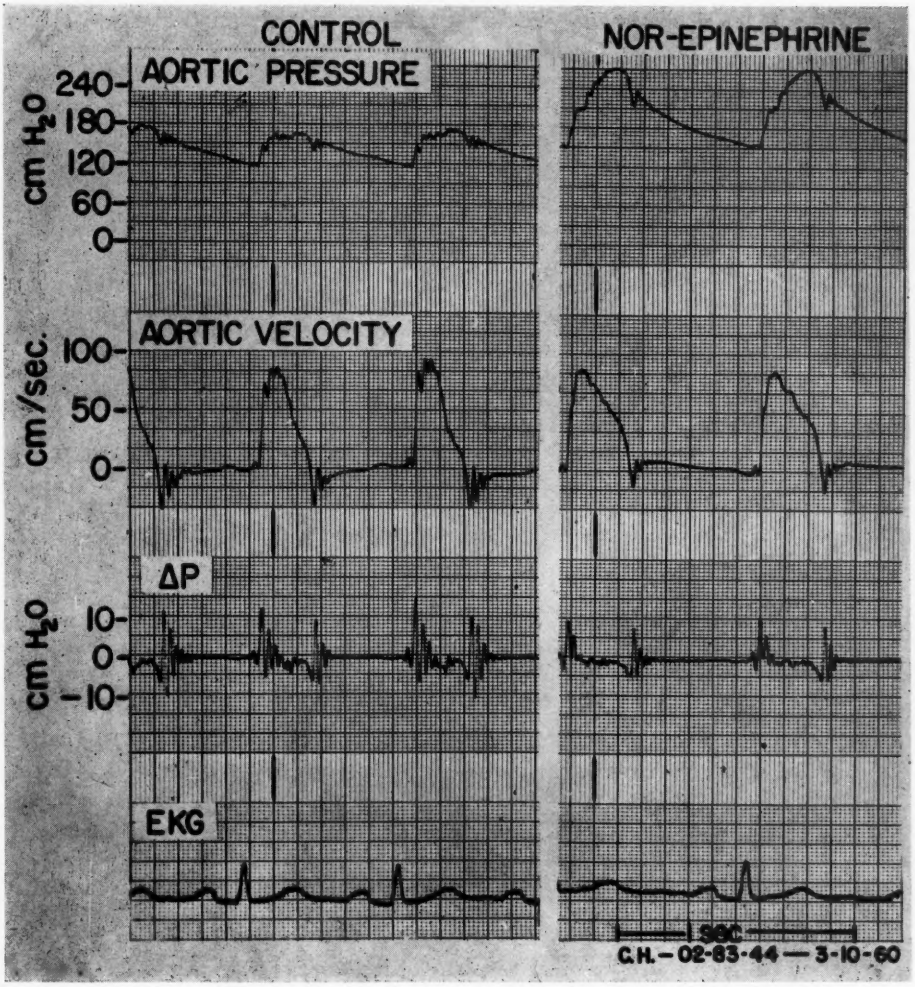

Fig. 5. A record of the effect of intravenous norepinephrine upon the central aortic pressure, computed blood velocity, and measured pressure difference in a presumably normal 46-year-old man.

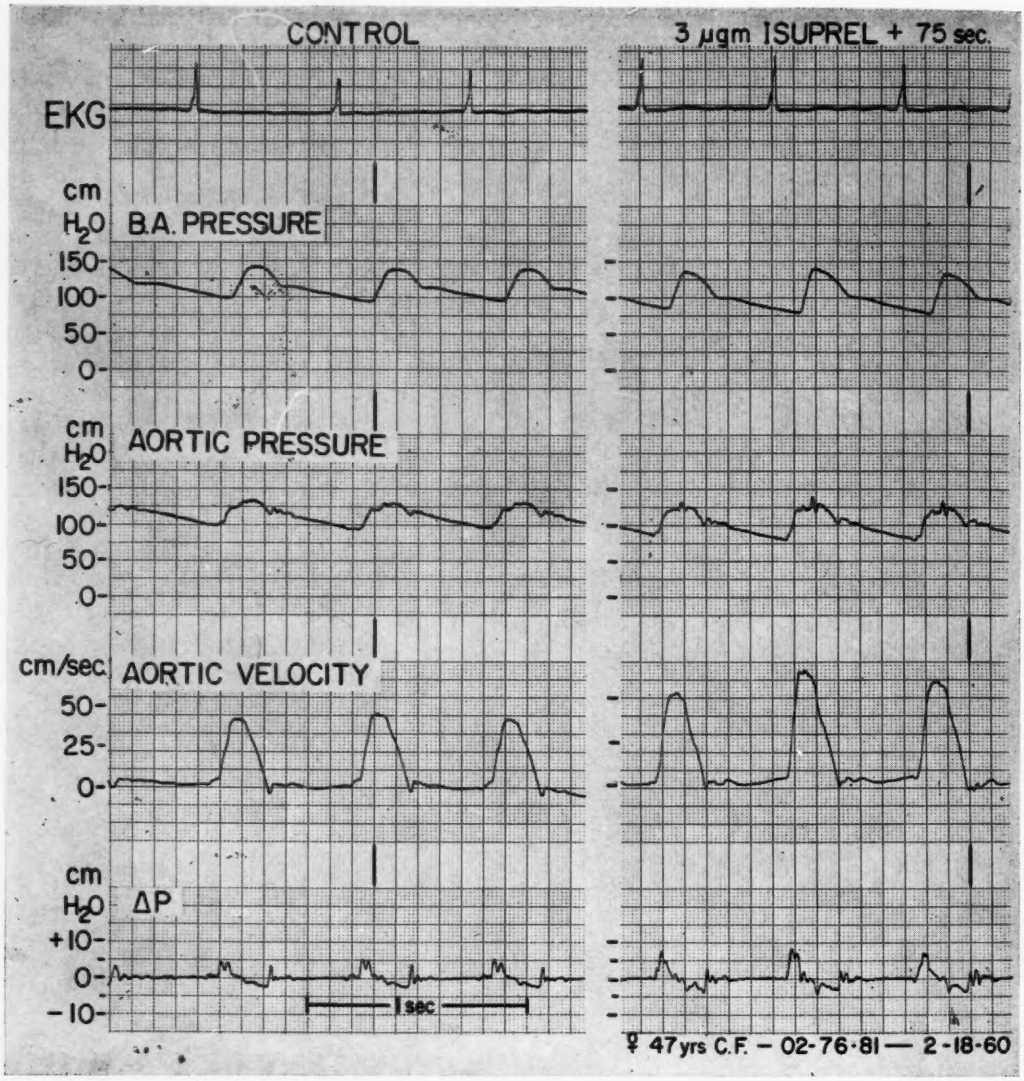

Fig. 6. A record of the effect of intravenous isoproterenol (Isuprel) upon the electrocardiogram, brachial arterial and central aortic pressure, computed aortic blood velocity, and measured pressure difference in a 47-year-old woman with known endocardial fibrosis.

tortion through frequencies up to 12 c.p.s. to obtain a useful pressure difference. In addition, we have arbitrarily required that the maximum difference between the response of each side of the system be less than 5 per cent of the driving pressure when the same sinusoidal pressure (through frequencies up to 12 c.p.s.) is applied to both lumens of the catheter. There may be significant information in the pressure difference contained in frequency components above 12 c.p.s., but with the present technique such information will be distorted.

By means of sterile techniques the catheter is removed from the glass tube, and the entire system is placed on the catheterization table. After adequate local anesthesia the femoral artery is entered percutaneously by a modified Robb needle. The catheter is advanced into the aorta, and the needle is pulled back over its proximal portion. Pressure to prevent bleeding from the site of puncture is usually required during the entire procedure. Every 3 to 5 minutes the catheter is flushed with a heparin-saline solution. Under fluoroscopic control the catheter is advanced until the tip is in the ascending aorta, approximately 3 to 5 cm. above the aortic valves. It is frequently necessary to advance or withdraw the catheter

slightly to place the pressure taps downstream from the aortic valves and upstream from the innominate artery so that the necessary hydrodynamic assumptions are met.[1] For the present, the chief criterion for correct position is that the computed velocity corresponds to zero during the latter part of diastole.

Application in the intact human being. In this section, data from a number of studies are presented. The finer details of the velocity contour must be interpreted with caution, since the coefficient of blood friction used in the velocity computation had to be chosen arbitrarily as previously presented.[1] The contour of the velocity curve in the ascending aorta of a presumably normal 46-year-old man is illustrated on the left side of Fig. 3. The velocity tracing obtained from a 32-year-old man with active myocarditis and congestive heart failure is shown on the right side of Fig. 3. This latter curve represents one of the more marked deviations from normal that we have observed. A mild mechanical alternans is more noticeable in the velocity tracing than in the aortic pressure curve. In a 46-year-old patient with known myocardial fibrosis, the rhythm spontaneously changed from normal sinus rhythm to atrial fibrillation, as shown in Fig. 4. A decrease in ejection velocity is noted when the diastolic filling time is shortened and/or "atrial loading" of the ventricle is lost.

Ejection velocity was also measured after the administration of various drugs which are known to alter the myocardial contractility and peripheral resistance. Norepinephrine is known to increase myocardial contractility[3] as well as to increase peripheral resistance, resulting in an increase in stroke volume with a minute output that may be unchanged or decreased.[4] As illustrated in Fig. 5, norepinephrine given intravenously in an amount necessary to raise the systolic blood pressure 90 cm. H_2O caused an increase in the duration of effective blood ejection as well as a

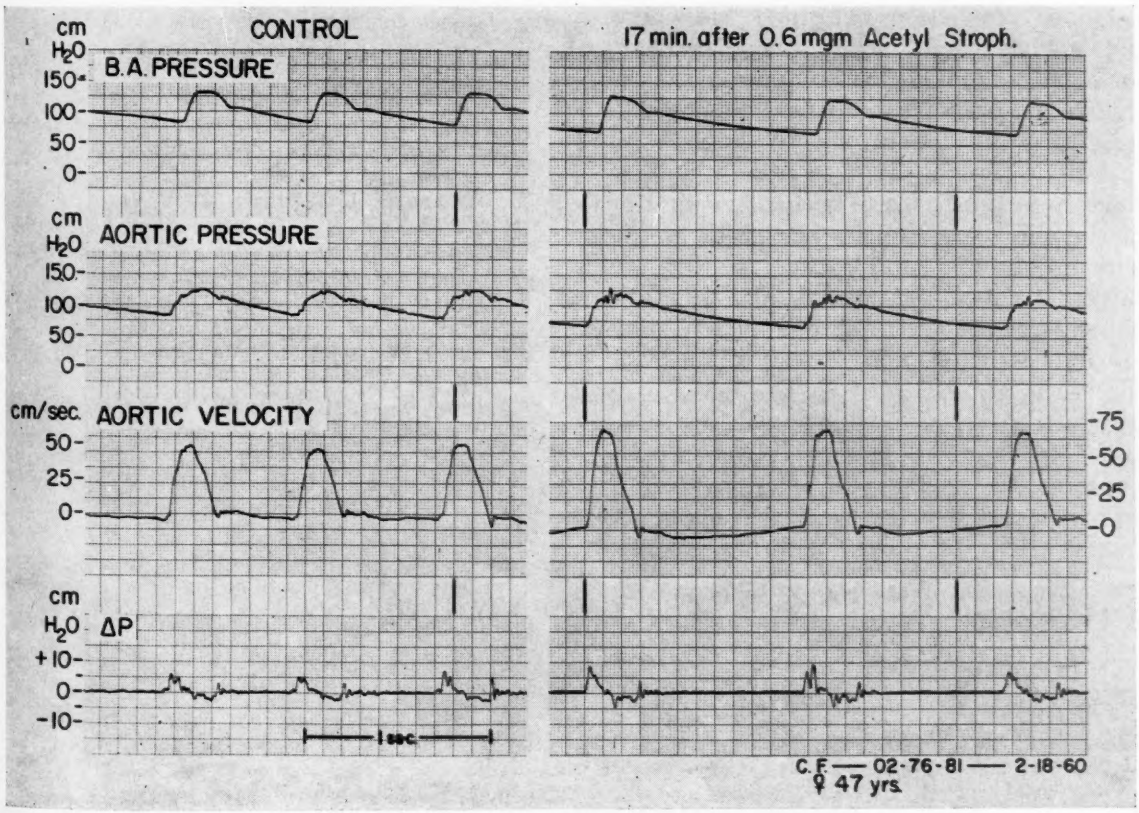

Fig. 7. A record of the brachial arterial and central aortic blood pressure, computed aortic velocity, and measured pressure difference obtained just prior to, and 17 minutes after, the intravenous administration of 0.6 mg. of acetyl strophanthidin to a 47-year-old woman with known endocardial fibrosis.

minimal decrease in peak ejection velocity. Isoproterenol has been shown[5] to cause an increase in heart rate and stroke volume. This is illustrated in Fig. 6; the administration of isoproterenol resulted in a marked increase in acceleration and peak ejection velocity, with a decrease in ejection time.

The administration of acetyl strophanthidin*—a rapid-acting digitalis preparation—to patients with congestive heart failure is known to cause a rapid increase in stroke volume and a slowing of the pulse.[6] It was observed that this agent usually caused a definite increase in ejection velocity. The increase in velocity was found in those patients with clinically evident myocardial insufficiency, and also occasionally in patients with no objective evidence of cardiac disease. Fig. 7 illustrates the change which occurred 17 minutes after the intravenous administration of 0.6 mg. of acetyl strophanthidin to a 47-year-old woman with known endocardial fibrosis.

Summary and conclusions

Under restrictions outlined elsewhere[1] the instantaneous aortic blood velocity may be estimated by computation from the spatial pressure gradient. The methods used in this laboratory to apply this technique to the intact human subject have been presented. The final evaluation of the clinical usefulness of this technique will require its application to a much larger number of normal and diseased subjects. However, these preliminary studies indicate that nonvalvular myocardial disease is accompanied by changes in the pumping mechanism which result in alterations in the ascending aortic blood velocity contour. The changes in ejection velocity which occurred after the intravenous administration of norepinephrine, isoproterenol, and acetyl strophanthidin are consistent with previously known information about these drugs.

We wish to acknowledge the encouragement and help of Dr. Donald L. Fry and Mr. Frank Noble, and the technical, nursing, and secretarial support of Clara V. King, Ray Kelly, Margaret M. Austin, Helen E. Hood, and Phyllis M. Stone.

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Addendum

Since acceptance of this manuscript for publication, Porjé and Rudewald, in Sweden, have published their studies[7] on the computation of aortic blood velocity in man by means of a differential pressure technique. In the derivation of their computation, the flow is assumed to be nonviscous, in contrast to the derivation[1] used in this study, wherein the viscous as well as the inertial forces are considered.

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Relationships between left ventricular ejection time, stroke volume, and heart rate in normal individuals and patients with cardiovascular disease

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Although considerable attention has been focused in recent years on the alterations in central pressure and blood flow in various cardiovascular diseases, there has been relatively little study of the temporal phenomena in cardiac contraction in these states. In 1904, Bowen[1] employed the carotid pulse tracing to assess the duration of left ventricular ejection in man. In 1926, Lombard and Cope,[2] applying this technique, observed an inverse relationship between heart rate and ejection time in normal human subjects. Later studies in animals demonstrated, in addition, a direct relationship between the cardiac stroke volume and ejection time.[3,4] In experimental studies of the ejection dynamics in various cardiovascular disorders, only the effects of acutely induced lesions have been studied.[4,5] Previous applications of these techniques to the study of ventricular ejection in patients with cardiovascular disease have not employed the indicator-dilution or the Fick principle in estimating the magnitude of the blood flow.[6,7] The ready availability of these techniques in the present-day cardiovascular laboratory, together with the stimulus provided by previous experimental studies, has prompted the current reinvestigation of these relationships.

Methods and materials

Observations were made in 60 normal male subjects who ranged in age from 23 to 64 years, and in 61 male patients with various forms of heart disease.

The cardiac output was determined by either the indicator-dilution method or the direct-oxygen Fick technique. When the indicator-dilution method was used, indocyanine green dye was injected through an intracardiac catheter into the superior vena cava or pulmonary artery. The concentration of indicator dye was continuously measured in peripheral arterial blood by withdrawal of blood through a cuvette densitometer by means of a constant-rate, motor-driven syringe. The amplified dye-dilution curve was recorded on a multi-

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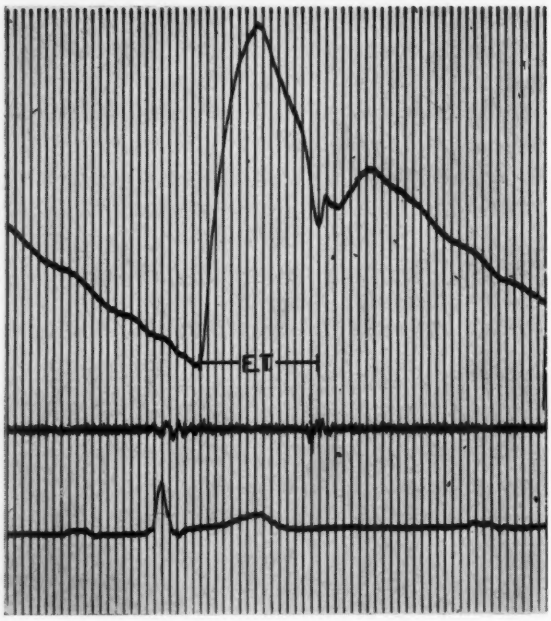

Fig. *1.* Simultaneous carotid pulse tracing, apical phonocardiogram, and electrocardiogram, illustrating the measurement of the ejection time from the upstroke to the incišura of the carotid pulse tracing. Time markings indicate 0.02-second intervals.

channel photographic unit from which analysis of the time concentration curve was made. When the Fick method was utilized, arterial and mixed venous (pulmonary artery) oxygen content was determined by the method of Hickam and Frayser.[8] The expired air was collected in Douglas bags over a 2 to 3-minute period, and the gas analyses were made by means of the Pauling oxygen analyzer. Simultaneous determinations of cardiac output by the two methods were made in 19 of the patients in the present series. The range of cardiac output was 2.81 to 7.27 L. per minute. With use of the Fick method as a standard, the indicator-dilution determinations varied an average of 4.6 per cent (S.D. ± 3.7 per cent), with a maximum variation of 12.7 per cent. No systematic difference between the two methods was observed. Since congestive heart failure was present in a large number of the patients studied, making estimations of nonedematous weight difficult, the cardiac outputs rather than the cardiac indices are reported. Stroke volume (S.V.) was derived from the cardiac output and heart rate.

The left ventricular ejection time (E.T.) was determined from external pulse tracings which were obtained by placing a standard funnel-shaped pickup externally over the point of maximum pulsation of either the carotid or subclavian artery. The signals were amplified through a strain-gauge or piezoelectric apparatus and recorded on a multichannel photographic unit. A standard electrocardiogram and an apical phonocardiogram were recorded simultaneously. All recordings were made at a paper speed of 100 mm. per second, with the time markers indicating 0.02-second intervals. The ejection time was measured from the beginning of the upstroke to the trough of the incisural notch (Fig. 1). Care was taken to obtain tracings which clearly delineated these points. By this technique, the duration of ejection could be determined accurately to the nearest 0.01 second. In each individual, 5 to 10 consecutive complexes were measured, and the average was recorded to the nearest 0.005 second. Beat-to-beat variation did not exceed 0.01 second over the respiratory cycle when the R-R interval remained constant. When auricular fibrillation was present, the R-R interval corresponding to the average heart rate during the determination of cardiac output was selected and the succeeding complex measured. The average of 5 to 10 such beats was recorded as the ejection time. The mean rate of left ventricular ejection (MRLVE) was calculated from the ratio S.V./E.T. and is expressed in milliliters per second of ejection. In all studies, a steady state, as evidenced from the monitored pulse rate and arterial pressure, was achieved during the determination of the cardiac output and ejection time. The pulse tracings were recorded immediately before and after the determination of the cardiac output.

Table I. *Comparison of ejection time from carotid pulse tracing and central aortic pressure curve*

Subject	*Ejection time (sec.) (central aorta)*	*Ejection time (sec.) (external carotid pulse tracing)*
F.T.	0.370	0.350
F.K.	0.320	0.310
W.R.	0.210	0.210
A.H.	0.265	0.265
N.H.	0.310	0.300

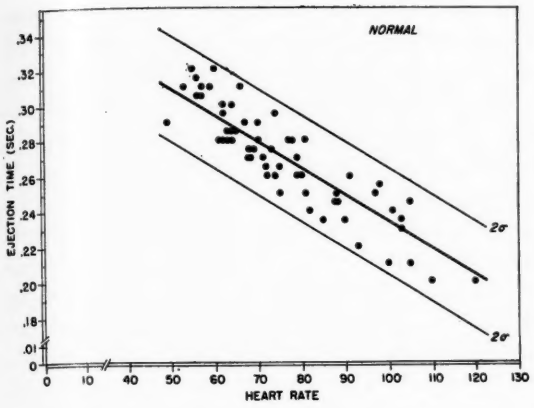

Fig. 2. Relationship between ejection time and heart rate in normal individuals.

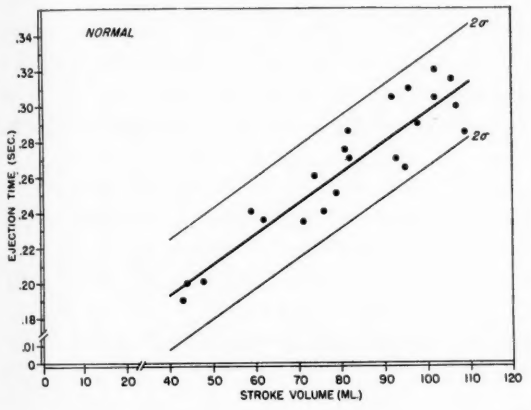

Fig. 3. Relationship between ejection time and stroke volume in normal individuals.

The ejection times derived from the simultaneous recordings of undamped central aortic pressure curves obtained by retrograde arterial catheterization and carotid or subclavian pulse tracings were compared in 5 individuals. A close agreement in the ejection times as determined by the two methods was observed (Table I), validating the measurement of ejection time from the pulse tracings as an index of left ventricular ejection time. The recording of brachial arterial pressure did not offer a reliable method for determining the ejection time because of the generally poor delineation of either the upstroke or the incisural notch in the tracings when fast paper speeds are employed.

All measurements of pressure were made by means of a Statham strain-gauge transducer (P23D). The zero level for pressures was taken as 5 cm. below the angle of the sternum when the subject was in the supine position. Respirations were recorded by means of a standard pneumograph.

Statistical analyses of the data were performed according to the methods of Snedecor.[9]

Results

Normal individuals. Observations on the duration of left ventricular ejection and heart rate were made in 60 normal, resting, supine male subjects; these included 52 hospitalized patients without cardiovascular disease and 8 normal university students. The relationship between the duration of ejection and heart rate is demonstrated in Fig. 2. As heart rate increased over the range of 49 to 120 beats per minute, the ejection time diminished linearly. The value for the correlation coefficient of $-.90$ was significant ($p < .01$).

Seventeen of the 60 normal subjects were selected for more detailed analysis of the relationships between ejection time, heart rate, stroke volume, and the mean rate of left ventricular ejection. In order to obtain observations at the lower levels of stroke volume, we studied 5 of these subjects in both the supine position and in the 45-degree head-up tilt position. The data are summarized in Table II.

As stroke volume increased from 43 to 109 ml., ejection time increased linearly (Fig. 3). The value for the correlation coefficient was $+.93$ ($p < .01$). The ejection time was likewise well correlated with the stroke index ($r = +.88$, $p < .01$). The

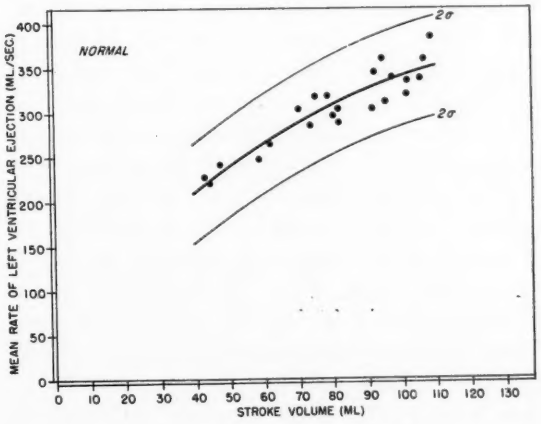

Fig. 4. Relationship between stroke volume and the mean rate of left ventricular ejection in normal individuals.

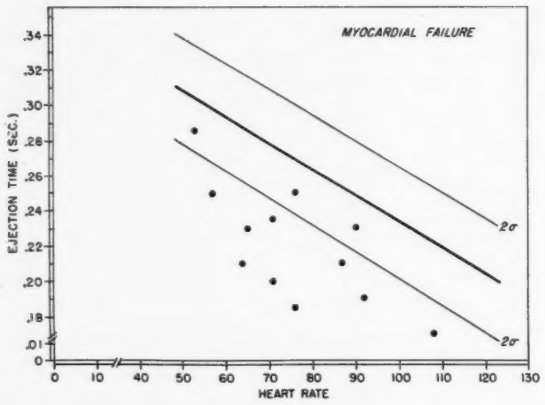

Fig. 5. Relationship between ejection time and heart rate in myocardial failure. The regression lines shown are those for the normal group.

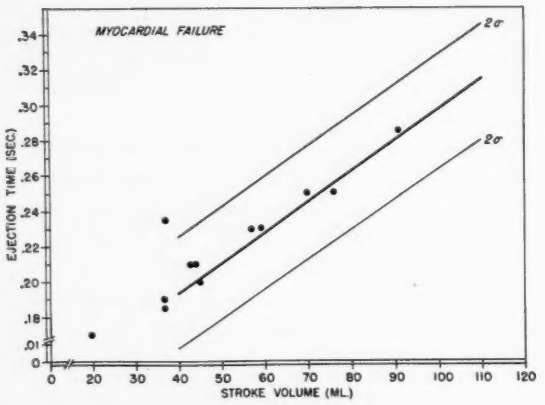

Fig. 6. Relationship between ejection time and stroke volume in myocardial failure. The regression lines shown are those for the normal group.

regression equations appear in Table III.

In Fig. 4 the relationship between stroke volume and the mean rate of left ventricular ejection (MRLVE) is shown. The MRLVE was derived from the relationship S.V./E.T. Over the normal range of stroke volume, the mean rate of left ventricular ejection varied from 220 to 382 ml. per second of systole and increased in a curvilinear fashion with stroke volume.

The relative contributions of the stroke volume and heart rate in the determination of the ejection time were further analyzed by multiple regression. The regression equation appears in Table III. It is apparent from this analysis that both stroke volume and heart rate contribute significantly to the ejection time in normal individuals.

Myocardial failure. The effect of myocardial failure and cardiac enlargement on the temporal dynamics of left ventricular ejection were studied in 12 patients with nonvalvular heart disease (Table IV). Etiologically, the patients fell into three groups: 4 with arteriosclerotic cardiovascular disease, 6 young adults with idiopathic cardiomegaly and heart failure, and 2 individuals with hypertensive-arteriosclerotic heart disease but with normal levels of arterial diastolic pressure at the time of study. All of the patients were males and demonstrated clear radiologic evidence of cardiomegaly. Six were classified clinically as having severe heart failure, and the other 6 had mild to moderate heart failure at the time of the study. All of the patients had normal sinus rhythm and normal QRS conduction on the electrocardiogram. Half of the patients were digitalized, whereas half had received no digitalis therapy prior to the study. The hemodynamic data are summarized in Table IV.

In Fig. 5, the relationship of heart rate and ejection time in the patients with myocardial failure is compared to the normal regression data. The cardiac output in this group ranged from 2.1 to 5.8 L. per minute, with a mean of 3.6 L. per minute. The heart rate ranged from 53 to 108 per minute, with an average of 76 (S.D. ± 16), representing no significant difference in heart rate from that of the normal group. Nine of the 12 patients demonstrated a significantly decreased ejection time relative to heart rate. Each of these 9 individuals had a cardiac output of 4.0 L.

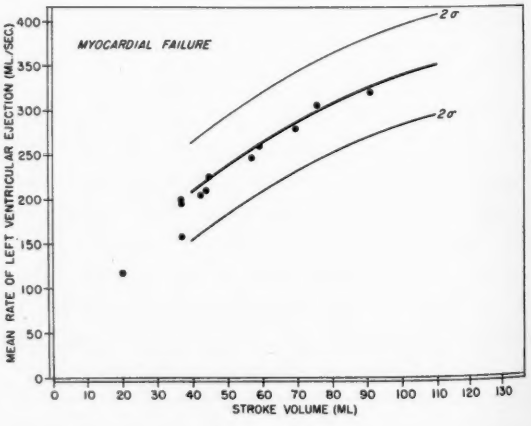

Fig. 7. Relationship between stroke volume and mean rate of left ventricular ejection in myocardial failure. The regression lines shown are those for the normal group.

or less. The decrease in ejection time relative to heart rate in the patients with heart failure was significant ($p < .05$).

The relationship between stroke volume and ejection time in the patients with myocardial failure is summarized in Fig. 6. When compared to the normal regression data, no significant difference was observed; the values for 10 of the 12 patients fell within the expected normal range of ejection time for stroke volume. The stroke volume rather than the stroke index was employed in this and subsequent comparisons, since the inclusion of an indeterminate amount of edematous weight in the calculation of the body surface area in patients with congestive heart failure may yield erroneous estimates of the stroke index. In 2 patients, rapid digitalization with deslanoside (Cedilanid), administered as a single dose of 1.6 mg. intravenously, induced slight increases in stroke volume 1 hour later (8 and 4 ml., respectively), while heart rate remained unchanged. At this time the relationship between stroke volume and ejection time remained within normal limits.

The relationship between the mean rate of left ventricular ejection and stroke volume for the 12 patients with myocardial failure is shown in Fig. 7. When compared to the normal regression data, no significant difference was apparent; the values for 11 of the 12 patients fell within 2 standard deviations of the normal regression line.

Aortic valvular disease. The relationship between ejection time and stroke volume was studied in 16 patients with aortic

Table II. *Hemodynamic data in normal subjects*

Subject	*Position**	*Cardiac output (L./min.)*	*Heart rate*	*Stroke volume (ml.)*	*Ejection time (sec.)*	*Mean rate of left ventricular ejection (ml./sec.)*
A.A.	S	5.58	68	82	0.270	304
J.P.	S	5.51	68	81	0.275	295
L.P.	S	5.23	85	62	0.235	264
H.W.	S	6.78	72	95	0.265	358
A.C.	S	4.79	49	98	0.290	338
C.W.	S	5.33	120	44	0.200	220
E.H.	S	5.94	56	106	0.315	337
S.I.	S	6.09	60	102	0.320	319
J.W.	S	6.31	66	96	0.310	310
D.W.	S	5.36	65	82	0.285	288
H.T.	S	5.17	56	92	0.305	302
J.G.	S	5.29	72	74	0.260	285
E.M.	S	6.65	62	107	0.300	357
	T	4.52	93	49	0.200	245
W.H.	S	6.31	68	93	0.270	344
	T	5.94	84	71	0.235	302
J.Y.	S	5.73	57	101	0.305	331
	T	4.70	80	59	0.240	246
H.R.	S	7.06	65	109	0.285	382
	T	5.63	74	76	0.240	317
S.W.	S	6.33	80	79	0.250	316
	T	4.29	100	43	0.190	226

*S: Supine. T: 45-degree head-up tilt.

Table III. *Summary of regression data in 17 normal male individuals*

E.T. = .266 − .0021 (H.R. −73)	$p < .01$
E.T. = .266 + .0017 (S.V. −82)	$p < .01$
E.T. = .266 + .0032 (S.I. −43)	$p < .01$
E.T. = .266 + .0011 (S.V. −82) − .0009 (H.R. −73)	$p < .01$ (S.V.) $p < .05$ (H.R.)

E.T.: Ejection time. H.R.: Heart rate. S.V.: Stroke volume. S.I.: Stroke index.

Table IV. *Hemodynamic data in patients with cardiovascular disease*

Patient	Diagnosis	Cardiac output (L./min.)	Heart rate	Stroke volume (ml.)	Ejection time (sec.)	Arterial blood pressure (mm. Hg)
		Myocardial failure				
D.W.	ASHD[d]	2.82	64	44	0.210	120/55
R.B.	ASHD	5.67	76	75	0.250	130/65
D.T.	ASHD[d]	3.19	71	45	0.200	120/74
J.E.	ASHD	2.81	76	37	0.185	122/85
S.H.	IMF	2.12	108	20	0.170	126/91
L.S.	IMF	5.35	90	59	0.230	142/98
O.B.	IMF[d]	2.47	71	35	0.235	105/69
A.W.	IMF[d]	3.70	65	57	0.230	158/85
R.P.	IMF[d]	4.01	57	70	0.250	107/64
F.C.	IMF[d]	3.41	92	37	0.190	120/78
E.C.	HASHD	3.72	87	43	0.210	174/83
J.C.	HASHD	4.86	53	92	0.285	163/73
		Mitral valvular disease				
L.H.	MS	4.52	79	57	0.230	127/87
H.Q.	MS–MI*	3.95	90	44	0.235	106/70
M.G.	MS–MI*	4.32	74	58	0.250	—
D.W.	MS–MI*	4.66	64	73	0.270	123/74
G.P.	MS	6.02	60	100	0.305	95/50
W.W.	MS–MI†	6.25	100	62	0.230	97/47
T.N.	MS–MI*	5.70	64	89	0.285	128/58
H.W.	MS–MI†	5.45	90	61	0.255	101/58
R.D.	MS	3.93	78	50	0.235	124/74
A.P.	MS–AI	4.00	56	71	0.320	108/50
I.H.	MS–AI	5.01	60	84	0.305	137/66
J.C.	MS–AI	3.35	52	64	0.300	136/63
		Aortic stenosis				
C.M.	RHD	6.11	63	97	0.325	—
L.S.	RHD	5.09	70	73	0.345	112/65
J.D.	RHD	4.22	54	78	0.380	108/62
S.B.	CAS	3.24	59	55	0.280	140/68
M.P.	CAS	2.91	70	42	0.270	123/64
		Hypertension				
J.W.	HCVD‡	3.93	88	45	0.230	225/115
D.S.	HCVD‡	2.97	75	40	0.205	174/104
D.H.	HCVD‡	2.69	62	43	0.195	171/115
B.S.	HCVD	6.59	69	96	0.260	256/123
H.W.	HCVD	6.27	92	68	0.205	250/136
W.R.	HCVD	5.05	72	70	0.270	211/122
H.W.	HCVD	5.93	83	71	0.225	192/104
H.F.	HCVD	6.90	74	93	0.255	230/134
R.W.	HCVD	4.80	89	54	0.200	217/149
W.S.	HCVD	5.20	52	100	0.260	220/124
W.J.	HCVD	6.63	90	74	0.215	160/104
		Aortic insufficiency				
C.F.	SHD	5.05	60	84	0.350	160/51
W.C.	SHD	4.10	55	75	0.365	162/38
C.P.	SHD	4.57	80	57	0.370	199/55
C.H.	SHD	3.55	62	57	0.280	138/43
H.H.	RHD	5.12	78	66	0.310	198/50
J.S.	RHD	6.44	55	117	0.335	132/61
J.S.	RHD	6.42	88	73	0.325	157/29
B.J.	RHD	6.05	65	93	0.320	121/59
F.T.	RHD	4.51	70	64	0.360	160/50
C.L.	RHD	5.94	54	110	0.315	134/70
W.C.	RHD	5.33	66	81	0.325	142/50
J.H.	ASHD	3.29	102	32	0.200	134/76
Z.J.	ASHD	3.45	57	61	0.290	160/48
B.W.	ASHD	3.11	61	51	0.290	136/59
J.A.	HCVD	4.34	69	63	0.300	210/88
J.C.	HCVD	3.22	72	45	0.255	225/122

*Mild mitral insufficiency.
†Moderate mitral insufficiency.
‡Hypertensive cardiovascular disease with myocardial failure.
ASHD: Arteriosclerotic heart disease. IMF: Idiopathic myocardial failure. HASHD: Hypertensive arteriosclerotic heart disease. HCVD: Hypertensive cardiovascular disease. MS: Mitral stenosis. MI: Mitral insufficiency. RHD: Rheumatic heart disease. CAS: Calcific aortic stenosis. SHD: Syphilitic heart disease. d: On digitalis at time of study.

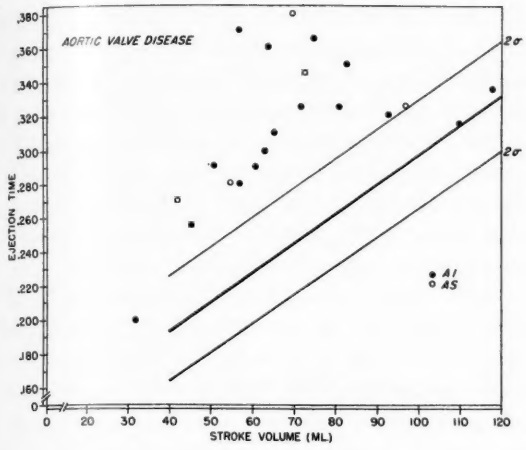

Fig. 8. Relationship between ejection time and stroke volume in aortic valvular disease. The normal regression lines are shown. *AI* denotes patients with aortic insufficiency; *AS* denotes patients with aortic stenosis.

insufficiency and in 5 patients with isolated aortic stenosis. Only patients who had pulse tracings which revealed accurate delineation of the upstroke and incisura were studied.

The patients with aortic insufficiency represented rheumatic, syphilitic, arteriosclerotic, and hypertensive etiologies. Ten of the group demonstrated obvious peripheral signs of aortic insufficiency, whereas in 6 a diastolic murmur was the sole clinical finding to indicate aortic regurgitation. None of the patients demonstrated auscultatory evidence of mitral stenosis or mitral insufficiency. The mean heart rate for the group was 68 (S.D. ±13), which represented no significant difference from the heart rate in the normal group.

In the 5 patients with aortic stenosis, objective evidence of stenosis was provided in 2 by retrograde arterial catheterization of the left heart, and in 1 by later postmortem examination. The other 2 patients demonstrated clear clinical signs of aortic stenosis without aortic regurgitation. The data are summarized in Table IV and Fig. 8.

Thirteen of the 16 patients with aortic insufficiency demonstrated a prolongation of the ejection time relative to stroke volume when values for them were compared to the normal data (Fig. 8). The 3 patients in whom the values fell within normal limits were among the individuals who demonstrated only the basal diastolic murmur of aortic regurgitation without peripheral signs. Each of the patients with aortic stenosis demonstrated prolongation of the ejection time relative to stroke volume.

The relationship of the pulse pressure to the degree of prolongation of the ejection time (observed value minus expected normal regression value for the stroke volume) for the 16 patients with aortic insufficiency is illustrated in Fig. 9. A significant correlation between the degree of prolongation of ejection time and the pulse pressure in aortic insufficiency was observed ($r = +.57$, $p < .01$).

In order to test further whether prolongation of ejection occurs in isolated aortic stenosis, we surveyed the literature to collect the cases of aortic stenosis for which stroke volume and systolic ejection periods derived from the aortic pressure pulse were published. The complete studies of Goldberg, Smith and Raber[10] on patients with isolated aortic stenosis offered an opportunity to compare our data in normal subjects with the data in 26 such patients who had calculated aortic valvular areas which ranged from 0.2 to 1.2 cm.^{2}. (Eleven of the patients in the Goldberg series in whom ejection time was estimated from the brachial arterial pulse were not included for comparison.) Twenty-two of the 26 patients with aortic stenosis demonstrated a prolongation of ejection time relative to stroke volume when their values were compared to the data for the normal group (Fig. 10). All of the patients with a cal-

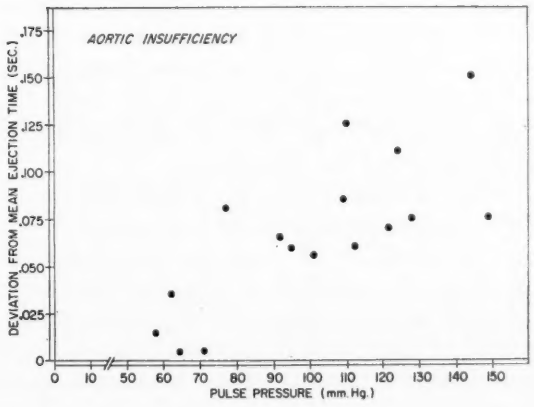

Fig. 9. Relationship between the degree of prolongation of ejection time and pulse pressure in aortic insufficiency.

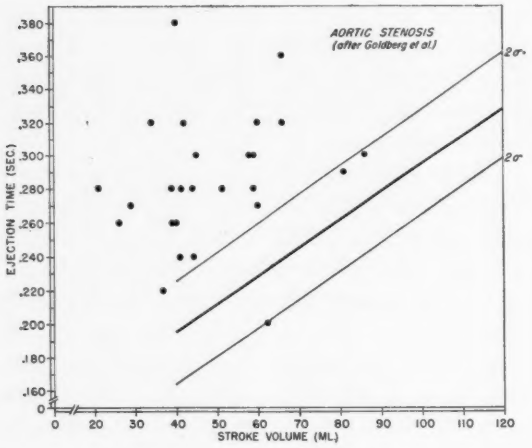

Fig. *10.* Relationship between ejection time and stroke volume in 26 patients with isolated aortic stenosis (from the data of Goldberg, Smith and Raber[10]). The regression lines are those for the normal group.

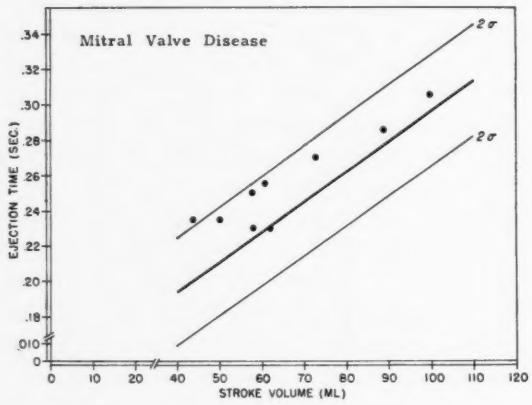

Fig. *11.* Relationship between ejection time and stroke volume in mitral valvular disease. The normal regression lines are shown.

culated valvular area of 0.5 cm.^{2} or less had a prolonged ejection time. Of the 4 patients with a normal ejection time, 2 had a calculated valvular area of 1.1 and 1.2 cm.^{2}, representing the largest calculated valvular areas for the group.

Mitral valvular disease. The relationship between ejection time and stroke volume was studied in 9 patients with mitral valvular disease. All of the patients were studied prior to surgical exploration and mitral valvulotomy. Evaluation of the function and size of the valve was performed at the time of valvulotomy. The area of the mitral valve was estimated to be 1.0 cm.^{2} or less in 7 of the patients, and 1.5 cm.^{2} in 2 of the patients. At the time of the operation the surgeon evaluated each valve for the presence of mitral regurgitation. Three of the patients demonstrated no palpable mitral insufficiency at the time of operation, whereas 4 had mild and 2 had moderate mitral regurgitation. In 3 of the group a basal diastolic murmur, thought to represent pulmonary insufficiency (Graham Steell), was heard.

The data are summarized in Table IV and Fig. 11. Four of the patients had cardiac outputs of 4.5 L. per minute or less, whereas the others had a cardiac output that was in the normal range. Auricular fibrillation was present in 5 of the patients. The mean heart rate for this group was 78 (S.D. ±15), which represented no significant variation from the normal data for cardiac rate.

Values for 8 of the 9 patients fell within normal limits with respect to the relationship of ejection time to stroke volume (Fig. 11). Although a tendency for the data to be distributed in the upper normal range of ejection time was noted, this represented no significant variation from the findings in the normal group.

Three additional patients with combined mitral stenosis and aortic insufficiency associated with wide pulse pressures were studied. Each of these individuals demonstrated a prolongation of ejection time relative to stroke volume.

Hypertension. The ejection time was studied in a group of 11 patients with severe hypertension (Table IV; Fig. 12). The systolic arterial pressure ranged from

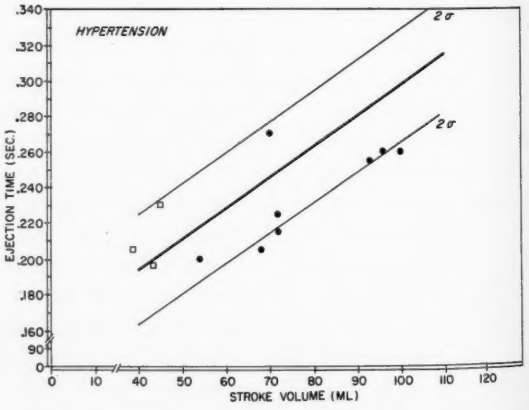

Fig. *12.* Relationship between ejection time and stroke volume in hypertensive disease. Patients with congestive heart failure are designated by the open squares. The normal regression lines are shown.

160 to 256 mm. Hg., whereas the diastolic pressure ranged from 104 to 149 mm. Hg. Eight of the patients had no clinical evidence of congestive heart failure, whereas 3 had clinically apparent signs of congestive heart failure at the time of the study. The mean heart rate of 77 (S.D. ±13) for the group was not significantly different from that for the group of normal individuals.

Fig. 12 illustrates the relationship between stroke volume and ejection time for the group compared to the normal regression data. The 8 patients without congestive heart failure all had normal cardiac indexes. Although 7 of these 8 patients tended to have a low ejection time relative to stroke volume, this represented no statistically significant variation from the findings in the normal group. The 3 patients with cardiac failure and hypertension were not included in the previous series of patients with myocardial failure. Each of these 3 individuals had values which fell within normal limits of ejection time relative to stroke volume.

Pericardial disease and pulsus paradoxsus. The respiratory effect on the ejection time in the presence of pericardial disease was studied in 2 patients with constrictive pericarditis and pericardial calcification (J.M., M.B.), and in 1 patient (W.P.) with pericardial effusion. The 2 patients with constrictive pericarditis demonstrated a variation in systolic arterial pressure of 28 and 34 mm. Hg, respectively, over the respiratory cycle at rest. The patient with pericardial effusion demonstrated a systolic variation of 6 mm. Hg during quiet breathing. In all 3 patients a significant change in ejection time, which ranged from 0.025 to 0.050 second, was noted through the respiratory cycle at a time when the R-R intervals remained constant (Table V). This change consisted of a serial shortening of the ejection time at the onset of inspiration, reaching a minimum just preceding the end of inspiration, and coinciding with the lowest systolic arterial pressure. In normal individuals studied during quiet respiration the left ventricular ejection varied no greater than 0.01 second when the R-R interval remained constant.

Discussion

The technique of recording the pulse tracing employed in this study offers a convenient means for assessing the duration of left ventricular ejection. It is of importance to emphasize that the duration of systole measured in this manner refers solely to the ejection or isotonic phase of cardiac contraction and does not include the periods of isometric contraction and isometric relaxation. Furthermore, the duration of ejection derived from the pulse tracing exceeds by a small time increment the true duration of isotonic shortening of the heart because of the slight delay in closure of the aortic valve.[3] Although this error in the time interval of ejection is a definite one, the interval between the termination of cardiac contraction and the closing of the aortic valve would appear to be sufficiently small relative to the over-all duration of ejection so as to not alter the data significantly.

Previous studies on the relationship between ejection time, heart rate, and stroke volume in human subjects and in patients with cardiovascular disease have employed

Table V. *Phasic respiratory variation in ejection time and blood pressure in patients with pericardial disease*

Patient	*End-inspiration*			*End-expiration*		
	Arterial blood pressure (mm. Hg)	*R-R interval (sec.)*	*Ejection time (sec.)*	*Arterial blood pressure (mm. Hg)*	*R-R interval (sec.)*	*Ejection time (sec.)*
J.M.	102/57	0.73	0.210	130/64	0.74	0.245
M.B.	150/80	0.78	0.220	184/90	0.78	0.270
W.P.	94/70	0.62	0.205	100/72	0.62	0.230

indirect measures of blood flow. The ready availability of techniques for the direct measurement of blood flow in the present-day cardiovascular laboratory prompted the present reanalysis of these relationships. The findings of a direct relationship between ejection time and both heart rate and stroke volume in normal, resting subjects is consistent with previous experimental observations.[3,4] In the isolated dog heart preparation, which permits convenient variation of individual cardiovascular parameters, Braunwald, Sarnoff and Stainsby[4] demonstrated that at any level of stroke volume there is an inverse relationship between ejection time and heart rate. Although isolation of the individual variables could not be achieved experimentally in the present study, the results of the analysis of the data by multiple regression is consistent with the dual role of stroke volume and heart rate in the determination of ejection time.

In patients with myocardial failure the ejection time was diminished relative to heart rate, and was normal relative to stroke volume. Since the range of heart rate in the patients with myocardial failure was comparable to that in the normal subjects, it would appear that the diminished ejection time reflects predominantly the low stroke volume in these patients. Of particular interest was the observation that, despite the presence of congestive heart failure and obvious cardiac enlargement, the relationship between stroke volume and the ejection time remained within normal limits in this group. In the course of experiments using the isolated supported dog heart preparation, a prolongation of ejection time has been observed when the descending limb of the ventricular function curve was reached.[4] The finding of ejection times within normal limits for stroke volume suggests that at least in this respect, in the present study, human congestive failure is not analogous to the state accompanying the descending limb of the Starling curve.

In the final analysis, the stroke volume during any given ejection time is a function of the mean rate of shortening of the myocardial fibers. When the left ventricular chamber is considered as a sphere, for any given amount of shortening per unit of time, a large chamber will eject a greater stroke volume than a smaller one. If a large chamber ejects the same stroke volume per unit of time as a small one, the over-all amount of shortening of the fibers of the large chamber must have been less. From such a theoretical analysis, and the observation of a normal relationship between stroke volume and ejection time in myocardial failure, it can be concluded that the degree of myocardial shortening per unit time, and thus the mean rate of left ventricular contraction, is diminished when compared to normal.

The finding of a normal relationship between stroke volume and ejection time in congestive heart failure permitted the analysis of the effects of various other cardiovascular disorders, such as aortic and mitral valvular disease and hypertension, on the dynamics of left ventricular ejection. The close agreement of heart rate in the studied groups with valvular disease when compared to normal would tend to dismiss heart rate as a significant factor in explaining the observed relationships between ejection time and stroke volume in these abnormal states. Prolongation of ejection time relative to stroke volume in patients with aortic stenosis was expected in view of the previous data of Katz and Feil,[11] demonstrating a prolonged ejection time relative to heart rate in these patients. Although the underlying mechanism for the prolonged ejection phase of contraction is not entirely understood, it is presumably related to the high outflow resistance and excessive myocardial load. The investigations into the effect of load on velocity of shortening of skeletal muscle by Fenn and Marsh[12] and A. V. Hill[13] are pertinent in this regard. These authors noted that the rate of shortening of skeletal muscle diminishes with increasing load. A decrease in the velocity of myocardial contraction on the basis of an excessive intraventricular load induced by the high outflow resistance could explain the prolonged ejection in aortic stenosis. The consistency of the finding of a prolonged ejection phase relative to stroke volume in the patients with severe aortic stenosis suggests the use of this relationship in the clinical evaluation of patients suspected of having this disease.

The prolongation of ejection time observed in experimentally induced[4] as well as clinically evident aortic insufficiency can be explained on a different basis. In aortic regurgitation the true cardiac stroke volume is greater than the peripheral or effective stroke volume. The duration of the aortic ejection is related to the true cardiac stroke volume, as was demonstrated in the normal data. Therefore, the prolongation of ejection time relative to the effective stroke volume can be attributed to the greater time spent in expelling the regurgitant volume. When the pulse pressure in the patients with aortic insufficiency was compared to the degree of prolongation of ejection, a significant correlation was found. Such considerations suggest future studies on the use of these relationships as a means of estimating regurgitant flow in patients with aortic insufficiency.

When the relationship between heart rate and ejection time is considered in patients with hemodynamically significant aortic valvular disease, prolongation of ejection time may not be observed in individuals with congestive heart failure. The decrease in ejection time relative to heart rate as a consequence of the low stroke volume in congestive heart failure may balance the prolongation induced by aortic valvular disease. Prolongation of ejection time relative to stroke volume in these patients is, therefore, a more predictable finding in the clinical analysis of these problems.

Previous studies in animals which attempted to assay the effects of hypertension have demonstrated a tendency for prolongation of ejection during sustained and severe increases in aortic pressure induced by mechanical outflow resistance.[4,5] The present findings were of interest in that none of the individuals studied demonstrated prolongation of ejection time. Rather, a normal and in some individuals a decrease in ejection time relative to stroke volume was observed. It is improbable, therefore, that the effects on left ventricular ejection of acutely induced aortic outflow resistance are comparable to the events in chronic hypertensive disease in human beings.

The observations on ejection time in patients with isolated mitral stenosis are consistent with the presence of normal left ventricular outflow dynamics in this disease. It is of note that gross prolongation of ejection, as was observed in aortic insufficiency, did not occur in the patients with mitral insufficiency. These observations suggest either that the regurgitant flow occurs at a very rapid rate relative to the aortic ejection or that the greatest volume of regurgitation occurs during the pre-ejection or postejection phases of ventricular systole. It is possible, however, that the magnitude of regurgitation in the patients studied was actually small relative to the peripheral stroke volume, since individuals with free mitral regurgitation were not observed in the present series. It is of interest that, in experimentally induced high-grade mitral regurgitation, left ventricular ejection was similarly unchanged.[4]

The present technique affords a simplified approach to the study of beat-to-beat changes in stroke volume. In this regard, the finding of a significant decrease in ejection time during inspiration in the patients with pericardial restriction, when heart rate remained constant, supports the thesis that a fall in stroke volume due to inspiration is the basis for paradoxical pulse.

Some further considerations relative to the temporal factors in cardiac contraction are worthy of notation. The relationships between heart rate, stroke volume, and ejection time are such that at a constant level of cardiac output the total duration of ejection per minute is greater at a high cardiac rate and low stroke volume than at a low heart rate and a high stroke volume. Excepting the minimum alterations in the duration of the isometric periods of contraction and relaxation which might occur with these changes in rate and stroke volume, the duration of diastole per minute is shortest at fast heart rates and low stroke volumes. Although these alterations in diastolic time might be of little consequence in normal individuals, they could play a significant role in patients with such conditions as mitral and tricuspid stenosis and coronary artery disease, in whom the duration of diastole becomes a more important determinant of ventricular or coronary artery filling.

During the course of the present studies, certain practical applications of the data have come to light. The recording of ejection time and heart rate alone may be of use in evaluating the level of cardiac output in patients with suspected heart failure, since a persistent decrease in ejection time relative to heart rate is indicative of a low stroke volume. In patients with a basal systolic or diastolic murmur, prolongation of ejection time relative to heart rate suggests hemodynamically significant aortic stenosis or aortic insufficiency. The technique may offer additional value in following up patients after operative procedures for these conditions. In view of the decrease in ejection time relative to heart rate occurring with congestive heart failure, the simultaneous determination of the cardiac output and stroke volume lends a greater specificity to the measurement of ejection time in the practical evaluation of patients with valvular heart disease.

Summary

In the present study the relationships between the ejection time, heart rate, and stroke volume in normal individuals and in patients with various cardiovascular disorders were investigated. Ejection time was measured from the carotid or subclavian pulse tracing, and stroke volume was derived from direct measurements of blood flow.

In normal individuals, ejection time varied inversely with heart rate and directly with stroke volume. In patients with nonvalvular heart disease and cardiac failure, ejection time was usually low relative to heart rate but tended to fall within normal limits relative to stroke volume. At the level of stroke volume observed in the patients with congestive heart failure, the mean rate of left ventricular ejection was within normal limits.

Prolongation of ejection time relative to stroke volume was observed in patients with aortic insufficiency and in those with isolated aortic stenosis. The degree of prolongation in ejection time was well correlated with the severity of the aortic valvular disease.

In patients with mitral valvular disease, including isolated mitral stenosis, as well as in those with mild to moderate mitral regurgitation, ejection time fell within the normal range relative to stroke volume.

In patients with severe hypertensive disease, ejection time fell within the normal or low normal range relative to stroke volume. In 3 patients with pericardial disease an abnormal phasic respiratory variation in ejection time was observed.

The present observations on temporal phenomena in cardiac ejection suggests the practical application of these techniques in the evaluation of patients with various cardiovascular disorders.

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Effect of expiratory and inspiratory breath-holding on the lead-field spatial vectorcardiogram

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After 50 years of electrocardiographic study there is still no unanimity of opinion concerning the fundamental cause of the changes in pattern observed during the respiratory cycle or at the extremes of expiratory and inspiratory breath-holding.

The earliest qualitative observations were those of Samojloff,[1] Einthoven,[2] and James and Williams,[3] but the first systematic studies were made by Einthoven, Fahr and de Waart,[4] Williams,[5] and Waller.[6]

By 1920, Lewis[7] had declared that "it is certain that the electrical axis bears to the anatomical axis a certain relation . . . and that the former may be employed within certain limits in calculating the actual lie of the heart in the body." But to what extent anatomic displacement could be regarded as responsible for the respiratory changes in the electrocardiogram he was less sure and added that "there are other factors which come into play, for accompanying the acts of breathing the vagal tone alters and the shapes of the curves are thereby influenced; some change is also induced in all probability by rotation of the heart around its own axis."

Since then many authors (e.g., Cohn and Raisbeck,[8] Herrmann and Wilson,[9] Master,[10] Burch, Abildskov and Cronvich[11]) have confirmed the dependence of the electrocardiogram on cardiac anatomic position, but, whereas most earlier workers had assumed that positional changes were chiefly responsible for the respiratory variations in pattern, subsequent investigators have tended to oppose that view and to implicate primarily nervous and hemodynamic factors. Woodruff,[12] on the basis of his own and Condorelli's[13] clinical observations, asserted that "the cause of the respiratory changes does not appear to be due to a shifting of the axis caused by movements of the diaphragm," and he invoked the influence of the vagus and sympathetic nerves, as well as variations in coronary blood flow, to account for the electrocardiographic findings.

In a recent study of the electrical changes during the respiratory cycle, Lamb[14] concluded that they could be correlated with expected differences in stroke volume of the right and left ventricles and were independent of varying cardiac position and autonomic nervous control. Similarly, Simonson, Nakagawa and Schmitt,[15] investigating the electrocardiographic patterns resulting from the more static conditions of expiratory and inspiratory breath-holding, were satisfied after statistical analysis that their data could not be explained adequately by anatomic factors alone.

In a detailed study during which he correlated functional residual volume with

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Table I. *Effect of breath-holding on mean heart rate and Q-T interval (Lead A)*

	R-R	*Heart rate*	*Q-T*	$\frac{Q-T}{R-R}$	QT_c
Normal respiration	0.87 sec. (S.D. 0.13)	69 per min. (S.D. 10)	0.37 sec. (S.D. 0.03)	0.43 (S.D. 0.05)	0.39 (S.D. 0.03)
Full expiration	0.86 (0.14)	70 (11)	0.36 (0.03)	0.43 (0.05)	0.39 (0.02)
	0.11 t = 5.8 p < 0.01	8 t = 5.7 p < 0.1		0.05 t = 6.1 p < 0.01	0.02 t = 6.1 p < 0.01
Full inspiration	0.97 (0.16)	62 (11)	0.36 (0.03)	0.38 (0.05)	0.37 (0.02)

Table II. *Effect of breath-holding on RLF-plane mean vector angles as determined from Limb Leads I and II*

	Normal respiration	*Full expiration*	*Full inspiration*
QRS	66° (S.D. 23)	61° (S.D. 30)	75° (S.D. 15)
	5° t = 2.6 0.02 > p > 0.01		15° t = 3.4 p < 0.01
T	42° (23)	35° (22)	50° (23)
	7° t = 3.8 p < 0.01		15° t = 5.0 p < 0.01
QRS-T	+24° (29)	+26° (34)	+25° (28)
VG	54° (18)	47° (19)	64° (13)
	7° t = 4.4 p < 0.01		17° t = 7.1 p < 0.01

cardiac electrical axis and radiologic appearance, Shephard[16] showed that normal quiet respiration produced a swing of 8 to 17 degrees in the frontal plane QRS vector (clockwise during inspiration), and that this degree of rotation on an anteroposterior axis was consistent with that observed radiologically. He also demonstrated that functional venesection by cuff occlusion produced minimal effects, suggesting that hemodynamics played only a minor part in determining the form of the electrocardiogram in his experiments.

Because of this conflict of opinion and the fact that almost all of the previous data have been obtained by means of the conventional RLF and chest leads, which are now known to possess inherent fundamental disadvantages, it was considered of value to reinvestigate this problem by employing the theoretically more satisfactory orthogonal lead-field system of

McFee and Johnston[17-19] and Jordan and Beswick[20] at the same time that a survey was being carried out to determine the normal ranges of scalar and loop spatial observations in a group of male medical students. Consequently, a study was made of the loop and vectorial effects produced at the extremes of expiratory and inspiratory breath-holding, to be followed later by further investigations during the more dynamic circumstances of the active respiratory cycle.

Method

Twenty-nine of the 47 subjects for whom lead-field scalar and loop spatial electrocardiographic data obtained during normal quiet respiration have been previously reported[20] were studied further by the same technique at the extremes of breath-holding.

After a period of relaxation and quiet breathing while lying supine, each subject was instructed to expire to the maximum short of physical straining and to hold the breath for about 10 seconds, during which time Leads I and II were synchronously recorded at fast paper speed (100 mm. per second) on a direct-writing Elema Elmqvist two-channel electrocardiograph. This process was repeated twice for recording the lead-field Leads A and B and B and C, and a further twice for photographing the frontal and horizontal planar loops from the screen of a vectorscope. Subsequently, similar records were obtained during breath-holding at maximal inspiration.

The methods for calculation of vectorial quantities and the symbols and orientations adopted for the presentation of the vectors and loops were the same as those previously described.[20]

Results

Of the 29 subjects examined, 23 were shown earlier[20] to comprise a single homogeneous group when assessed on the basis of cardiac vectorial and spatial loop analysis, whereas the other 6 showed individual pecularities. Consequently, although we have included all 29 students in the time-interval data of the present investigation, the mean vectorial values have been presented for the group of 23, and those for the other 6 have been treated separately.

Detailed analyses of the time intervals for all three orthogonal leads (A, B, and C) were made, but only the results from Lead A are reported as being typical of all three leads and roughly comparable with the conventional RLF-plane Lead I. The theoretical limitations involved in deducing time intervals from a single lead, instead of from the ideal arrangement of three synchronously recorded orthogonal leads, have been stressed by Pipberger and Tanenbaum[21] and Beswick and Jordan,[22] but for comparative assessment of the cardiac responses induced by changes in physiologic environment it would appear that some valid information can be obtained from a single lead.

The effects of respiratory changes on the mean heart rates for all the subjects are shown in Table I. There was no significant difference between the rates during quiet breathing and those with the breath held in full expiration, but when the breath was held in full inspiration, a mean decrease of 8 beats per minute was observed.

The duration of the Q-T interval was the same in all three respiratory states but, as a consequence of the increase in length of the cardiac cycle (R-R), the ratio $\frac{Q-T}{R-R}$ was significantly decreased in full inspiration. The "corrected Q-T interval (QT_c)" of Bazett,[23] i.e., $\frac{Q-T}{\sqrt{R-R}}$, which is commonly supposed to be constant irrespective of physiologic changes in heart rate, was in this study also reduced in full inspiration.

From Table II it appears that in the RLF plane, as calculated from Leads I and II, there are progressive shifts in vectorial position for both QRS and T, and, therefore, for the ventricular gradient (VG), from full expiration through quiet respiration to full inspiration; both vectors become more vertical by equal increments and thus leave the QRS-T angle unaltered.

Previously it has been shown that in both untrained students[24] and international athletes[22] the majority of subjects breathing quietly give RLF-plane vector angles which can be converted to the corresponding frontal plane values, as given by the lead-field technique, by using a simple right-angled isosceles triangular reference frame

Table III. *Frontal plane mean vector angles derived from RLF-plane data using a right-angled isosceles triangular reference frame*[24]

	Normal respiration	*Full expiration*	*Full inspiration*
QRS	58° (S.D. 18)	56° (S.D. 22)	64° (S.D. 12)
		8°	t = 3.1 p < 0.01
T	55° (15)	51° (14)	61° (16)
	4° t = 3.3 p < 0.01		10° t = 5.2 p < 0.01
QRS-T	+ 3° (21)	+ 5° (24)	+ 3° (21)

instead of the Einthoven equilateral. The data given in Tables III and IV demonstrate that this interconversion holds good in the conditions of extreme breath-holding studied here, since there are no statistical differences between the calculated and the observed vectorial angles.

Since it can be seen from Tables IV and V that the lead-field cardiac vectorial values were the same in both spatial direction and magnitude during quiet respiration and at full expiration, all further statistical comparisons have been made only between the two extreme states of breath-holding.

There was no significant difference between the mean spatial QRS-T angles calculated for inspiration and those for expiration (Table IV), although the T vector became more vertical and anteriorly directed in inspiration. At the same time, the QRS vector moved only downward and through a smaller angle than T. Therefore, the QRS-T angle in the frontal plane was reduced, and in the horizontal plane increased in inspiration, with VG moving in the same sense as T.

The mean spatial magnitudes for T and "total QRS" were both reduced in inspiration (Table V) by about 10 and 8 per cent, respectively, leaving their ratios unaffected.

Fig. 1 shows typical planar vectorcardiographic loops which illustrate the effects of the contrasting respiratory states, and it is apparent that, in general, inspiration produced more vertical QRS loops, coupled with some anticlockwise rotation on a longitudinal axis and anterior displacement of the T loops. In addition, for the majority of subjects, smaller voltages were recorded from the body surface during inspiration.

The vectorial data for the 6 subjects of the subsidiary group are given in Table VI, and representative planar loops are illustrated in Fig. 2. These findings are considered separately at the end of the following discussion and compared with those of the main group.

Discussion

Main group of 23 subjects. The well-known increase in heart rate associated with the act of inspiration is not maintained if the breath is held at the height of inspiration. The reduced mean rate of 8 beats per minute observed in the present study confirms the conclusion of Lamb[14] and Lamb, Dermksian and Sarnoff[25] that this is the most common response to breath-holding at maximum voluntary lung inflation, but the greatest individual reduction noted was only 20 beats per minute in contrast to the 50 quoted by those authors. It should be emphasized that a reduction in rate was not an invariable finding, since approximately 10 per cent of our subjects showed a small increase.

Table IV. *Effect of breath-holding on the lead-field frontal and horizontal planar and spatial mean vector angles*

	Normal respiration	*Full expiration*	*Full inspiration*
		Frontal Plane	
$F\hat{A}_{QRS}$	60° (S.D. 17)	62° (S.D. 17)	66° (S.D. 14)
		4°	t = 2.2, p < 0.05
$F\hat{A}_{T}$	55° (15)	55° (15)	64° (15)
		9°	t = 5.7, p < 0.01
$F\hat{A}_{QRS\text{-}T}$	+ 5° (21)	+ 7° (21)	+ 2° (20)
		5°	t = 2.6, p < 0.01
$F\hat{A}_{G}$	59° (11)	59° (12)	67° (11)
		8°	t = 6.0, p < 0.01
		Horizontal Plane	
$H\hat{A}_{QRS}$	298° (20)	296° (20)	295° (20)
$H\hat{A}_{T}$	71° (11)	71° (12)	77° (10)
		6°	t = 6.0, p < 0.01
$H\hat{A}_{QRS\text{-}T}$	+133° (24)	+135° (24)	+142° (24)
		7°	t = 4.3, p < 0.01
$H\hat{A}_{G}$	52° (17)	54° (19)	60° (18)
		6°	t = 5.5, p < 0.01
		Spatial	
$(SP)\hat{A}_{QRS\text{-}T}$	+102° (17)	+104° (17)	+105° (21)

Table V. Effect of breath-holding on the lead-field mean spatial vector magnitudes (in microvolt-seconds)

	Normal respiration	*Full expiration*	*Full inspiration*
$(SP)A_{QRS}$	34 (S.D. 13)	34 (S.D. 13)	33 (S.D. 12)
$(SP)A$"total $_{QRS}$"	53 (17)	52 (17)	49 (16)
		3	t = 4.8, p < 0.01
$(SP)A_T$	85 (26)	86 (27)	76 (28)
		10	t = 3.3, p < 0.01
$\frac{(SP)A_T}{(SP)A\text{"total }_{QRS}\text{"}}$	1.7	1.8	1.7

The usual response is attributed by Lamb and associates[25] to reflex vagal slowing when stretch receptors in the lung tissue or visceral pleura are stimulated. If this is the case, it is possible that those subjects who showed an increase in pulse rate may have reduced the stretch stimulus by closing the glottis and relaxing the inspiratory activity of the thoracic musculature, thus compressing the lung gases to a volume less than that of maximal inflation, whereas the others had maintained maximal inflation with the glottis open.

The duration of the Q-T interval is of some importance since it can be regarded as an approximate measure of mechanical ventricular systolic time, and its mean value in the present study was found to be unchanged with respiratory state at 0.36 second (Table I) in spite of the difference in heart rate. This constancy of Q-T for the individual at heart rates within the physiologic range was noted by Shipley and Hallaran[26] during sinus arrhythmia, and confirmed by de Lalla and Brown[27] in subjects at the peaks of expiratory and inspiratory efforts.

With the increased length of cardiac cycle observed during breath-holding at full inspiration it follows that the ratio $\frac{Q-T}{R-R}$ must decrease, but the reduction from 0.43 to 0.38 may not be wholly due to the decrease in heart rate per se, since, when $\frac{Q-T}{R-R}$ is plotted against R-R, there is some evidence to suggest that at a given cycle length the ratio is smaller during full inspiration than during full expiration.

In a previous study[22] it was shown that the QT_c of Bazett,[23] which was originally introduced to eliminate changes in Q-T with heart rate, was, in fact, different for the highly trained athlete as compared with the untrained subject. The present data indicate that it also varies with the respiratory state, and it would appear, therefore, that it fails to fulfill its purpose.

The primary reason for this investigation was to re-examine the theses that respiratory changes in the electrocardiographic record can be adequately explained by shift in cardiac anatomic axis alone or by varying hemodynamic conditions within the thorax, or by a combination of both these factors.

The early observations of Einthoven, Fahr and de Waart[4] that the electrical axis of QRS became more vertical by approximately 20 degrees, and that of T by 15 degrees, in the change from expiration to inspiration were attributed solely to a corresponding change in cardiac anatomic position, but, subsequently, opin-

ion has tended to favor the view that this simple explanation is inadequate and that the electrical events in the heart are also affected by the interplay of respiratory and cardiovascular forces.

The latest quantitative conventional lead studies on 38 male subjects by Simonson, Nakagawa and Schmitt[15] appear to support the conclusion of Lamb[14] that "the changes are not due to a simple shift in anatomic position of the heart" but are dependent on hemodynamic factors which result from variations in intrathoracic pressure at different phases of respiration. Simonson and associates based their contention on the claim to have demonstrated a significant increase in spatial QRS-T angle during inspiration, which is unlikely to occur as a result of shift in cardiac position. However, the technique employed by those workers involved the use of RLF-plane limb and standard chest leads, which, although hallowed by universal clinical acceptance, are not sufficiently accurate, especially in the anteroposterior axis, for the determination of spatial vectorial angular values. In addition, the difference in spatial QRS-T angle of approximately 5 degrees between full expiration and inspiration given by Simonson is of doubtful statistical significance.

The results for a preliminary determination of the RLF planar angles in the present study (Table II) show trends similar to those reported by Simonson and associates,[15] except that both QRS and T vectors are more vertical by about 20 degrees at all phases of respiration. This discrepancy may to some extent be attributable to the greater mean age (43 years) and very wide range in age (19 to 63 years) of Simonson's subjects, since it has been shown that with increasing age both QRS and T vectors become more horizontal.[28] In this plane the QRS mean vector angles increased by approximately 15 degrees during breath-holding at full inspiration, and those subjects whose electrical axes were most horizontal in expiration showed the greatest angular increase. The mean T vector angle was affected similarly, so that the QRS-T angle in the RLF plane remained constant.

In addition to their RLF-plane data, Simonson, Nakagawa and Schmitt[15] determined the respiratory changes in vectorial angles, using several of the current "orthogonal" vectorcardiographic techniques, especially the SVEC-III system of Schmitt and Simonson.[29] This method employs vertical and horizontal lead electrode placements which, in general, are similar

Table VI. *Effect of breath-holding on the lead-field vector angles for the subsidiary group of 6 subjects*

Subject		*Frontal plane*				*Horizontal plane*				*Spatial QRS-T*
		QRS	*T*	*QRS-T*	*VG*	*QRS*	*T*	*QRS-T*	*VG*	
A	Exp.	67°	56°	+11°	61°	26°	65°	+39°	57°	+41°
	Insp.	70°	54°	+16°	62°	28°	71°	+43°	65°	+48°
B	Exp.	149°	47°	+102°	51°	124°	44°	−80°	51°	− 71°
	Insp.	185°	53°	+132°	57°	150°	50°	−100°	56°	−100°
C	Exp.	344°	35°	−51°	19°	338°	71°	+93°	60°	+93°
	Insp.	11°	34°	−23°	23°	347°	81°	+94°	71°	+94°
D	Exp.	13°	71°	−58°	65°	56°	54°	−2°	55°	+52°
	Insp.	47°	79°	−32°	75°	40°	61°	+21°	56°	+29°
E	Exp.	63°	66°	−3°	65°	348°	54°	+66°	33°	+35°
	Insp.	65°	65°	0°	65°	344°	51°	+67°	30°	+33°
F	Exp.	55°	71°	−16°	60°	299°	81°	+142°	351°	+108°
	Insp.	60°	80°	−20°	64°	299°	87°	+148°	4°	+105°

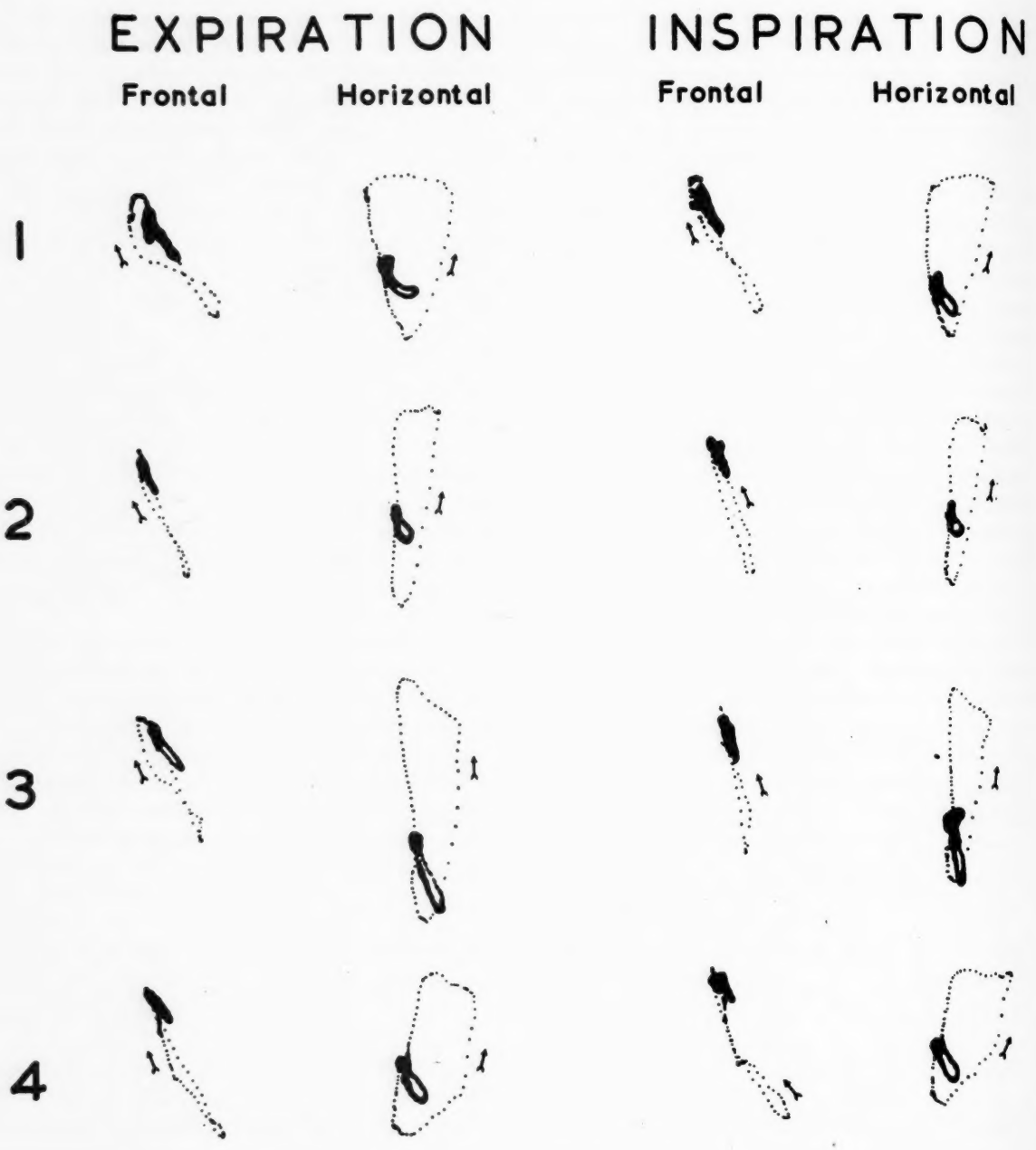

Fig. *1.* Frontal and horizontal lead-field planar loops for four typical subjects of the main homogeneous group.

to those of the lead-field technique, but the results recorded even in the frontal plane during normal quiet respiration differed markedly from those of the present study. The mean vector angles for 200 normal subjects[29] were 23 degrees for QRS and 26 degrees for T, as compared with the 60 and 55 degrees, respectively, given in Table IV. However, Pipberger,[30] also using the SVEC-III system more recently, has established what he terms the "preliminary standards" for the method at 41 degrees for QRS and 44 degrees for T in the frontal plane, which obviously approximate more closely those of the lead-field system.

Similar differences in vector orientation are manifest by the two methods in the horizontal plane, where the narrow $H\hat{A}_{QRS-T}$ of Schmitt and Simonson (36 degrees) is increased by Pipberger to 75 degrees and further to 133 degrees in our lead-field study during normal respiration,[20] due to approximately equal displacements of QRS posteriorly and T anteriorly. The cor-

responding (SP)$\hat{A}_{QRS-T}$ values were 56 degrees (S.D. 19) according to Ball and Pipberger[31] and 102 degrees (S.D. 17) for our subjects.

Although it is difficult to account for the divergent results of the two sets of investigators using the SVEC-III method, there are some obvious factors which could have contributed to the differences between the results given by that system and those of our lead-field technique. In the first place, the average age of our subjects was about 17 years less than that of Pipberger's,[30] and the method of lead weighting adopted in the SVEC-III approach would have the effect of reducing the apparent spatial (and, therefore, horizontal planar) QRS-T angle. Furthermore, to calculate their vector angles, Ball and Pipberger[31] utilized the projections onto rectangular coordinates of the instantaneous deflection which bisected the spatial vector loop, although it was recognized[30] that this procedure was open to serious criticism, since it not only neglects entirely the total time occupied by the cardiac electrical activity but also assumes that the loop is inscribed symmetrically with respect to time. The errors inherent in that method of computation are eliminated by using the voltage-time units derived from algebraic summation of areas enclosed by scalar deflections from orthogonal leads, as was done in the present study.

Notwithstanding these quantitative differences between the SVEC-III and lead-field techniques, it would have been anticipated that qualitatively similar vectorial trends would have been apparent as a result of varying the degree of pulmonary inflation. Simonson and associates[15] claimed to have demonstrated in 22 male subjects a more significant mean increase of 16 degrees in (SP)$\hat{A}_{QRS-T}$ on full inspiration than was suggested by their RLF-plane and chest-lead analysis, and they regarded this finding as conclusive evidence in favor of their thesis that factors other than purely anatomic ones were involved.

The results presented in Table IV, on the other hand, do not support their conclusion that there is a significant alteration in spatial QRS-T angle with change in respiratory state, although there were differences in the planar projections. In the frontal plane, both QRS and T vectors became more vertical on inspiration, but T to a greater extent by 5 degrees, so that it came to lie directly anterior to QRS, as would occur if, at the same time

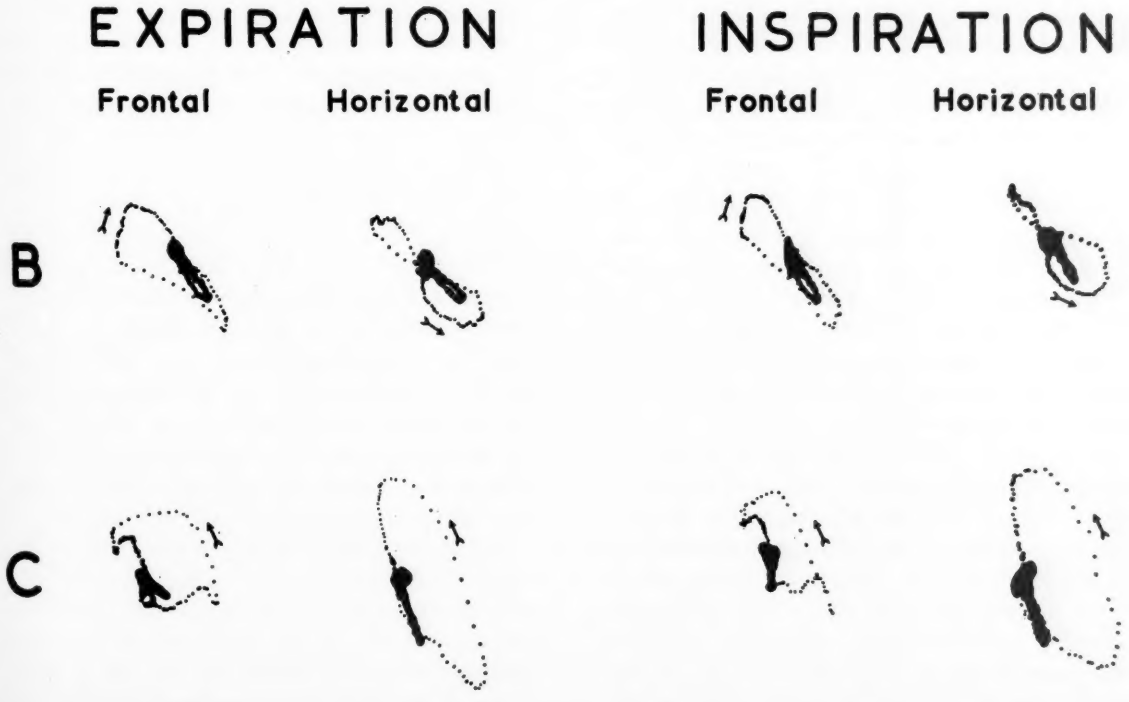

Fig. 2. Frontal and horizontal lead-field planar loops for two subjects (B and C) of the subsidiary group.

as the heart were rotating clockwise on an anteroposterior axis, it also rotated anticlockwise (as viewed from below) around a hypothetical longitudinal axis directed downward and to the left. In the horizontal plane the mean direction of the QRS vector remained constant, whereas the T vector became more anterior during full inspiration, suggesting that the axis of longitudinal rotation was also directed posteriorly, i.e., it was more closely related in space to QRS than to T.

This interpretation of the vectorial spatial positional changes is supported by the alterations in the planar contours of the lead-field vector loops with differing respiratory state, as shown in Fig. 1. In the frontal plane the QRS loop is seen to become more vertically oriented and apparently rotated anticlockwise around a longitudinal axis at full inspiration.

In the particular experimental circumstances reported here, therefore, with supine subjects at the two extreme conditions of breath-holding, the vectorial angular changes could be adequately explained simply by the assumption of a combination of anatomic rotations of the heart around anteroposterior and longitudinal axes.

Although there was no significant change in spatial magnitude of QRS (as conventionally determined by algebraic summation of deflections), there were reductions at full inspiration in "total QRS" (as previously defined[20]) and T magnitudes, principally due to decrease in voltage rather than in duration of activity.

It is already well known that the resistivity of lung tissue varies with the degree of its inflation, the specific resistance increasing with the content of air,[32,33] but the extent of the increase in resistivity also depends on the frequency of the electrical signal[34] becoming progressively greater the lower the frequency.

Since the effect of inspiration on the spatial vectorial magnitudes in the present study was found to be more pronounced during the lower frequency repolarization component of the electrocardiogram, it suggests that this resistivity factor may be exerting an influence, although, because the three orthogonal leads of the lead-field system are likely to be affected equally, the spatial positions of the vectors will be unaltered in spite of the changes in magnitudes.

So far, consideration has only been given to the direct effects on the heart of changes in lung inflation, but indirect factors of cardiovascular origin may also theoretically be concerned. That pulmonary hemodynamic variations during the respiratory cycle modify the QRS complex has been demonstrated by Lamb,[14] and this modification may be due partly to the changes in diastolic intracavitary blood mass which result from fluctuating atrial filling pressures, with consequent variation in the electrical short-circuiting effects described by Brody[35] and discussed by Beswick and Jordan.[22] In the more static respiratory conditons investigated here at the extremes of breath-holding, however, there will be no rhythmic variation in atrial filling pressure, but it is possible that the end-diastolic volume may be different in the two states of lung inflation, and that this might have influenced the spatial position of the QRS vector. In fact, this position remained constant relative to T, and, therefore, the "Brody effect" appears to have been unimportant. The constancy in shape of the inspiratory and expiratory *spatial* QRS loops also suggests that there was no marked right-sided or left-sided overloading in either phase (see Cabrera and Gaxiola[36]).

Subsidiary group of 6 subjects. Of these 6 subjects whose unusual loop and vectorial patterns distinguished them from the main group, one (Subject F) differed only in respect to the configuration of his spatial QRS loop, which exhibited none of the usual early anteriorly directed electrical activity, but vectorially he showed exactly the same respiratory changes as the majority of subjects. At present, the only tentative interpretation that can be offered for this peculiarity is the possible existence in this heart of an uncommon time-course for the early stages of depolarization which produced a loop contour resembling that of a relative physiologic left-sidedness.

All of the other 5 subjects were characterized by anterior displacement of the QRS vectors to an extent which separated them statistically from the main group and was possibly due to some degree of relative right ventricular preponderance. On the other hand, it should be noted that the

orientation of T in these individuals did not differ significantly from that in the majority, and, therefore, the vectorial pattern was not likely to be pathologic.

Three of the 5 had spatial QRS-T angles which were not affected by changes in lung inflation, and in all 5 there was the usual clockwise rotation about an anteroposterior axis, but the position of the QRS and T vectors in the frontal plane suggested *clockwise* rotation at inspiration about a longitudinal axis, i.e., opposite to that usually observed. However, inspection of their frontal plane QRS loops showed that those of Subjects A, B, and E were rotated *anticlockwise* from expiration to inspiration; that of Subject C, who had the most marked left axis deviation of all the 29 students examined, was rotated *clockwise*; whereas the result for Subject D was equivocal. It would appear, therefore, that the hearts of these individuals with unusually anteriorly directed QRS vectors are also, in general, displaced anticlockwise anatomically around a longitudinal axis, but that some unknown, possibly hemodynamic, factor complicated the apparent rotation, as determined from the mean spatial vectors.

Summary and conclusions

Twenty-nine male medical students were examined by the lead-field vectorcardiographic technique during breath-holding at full expiration and full inspiration, and the spatial vectorial results and planar loops were compared with those previously obtained during normal quiet respiration.

For 27 out of 29 subjects the mean spatial QRS-T angle did not change with respiration, although the majority showed marked clockwise rotation of frontal plane vectors and loops during inspiration, with, in addition, evidence of anticlockwise rotation around a longitudinal axis directed downward to the left and posteriorly. At inspiration the mean "total QRS" and T voltages were reduced.

The significance of these findings is discussed in relation to the parts played in their causation by anatomic positional shifts in the heart and variation in hemodynamic conditions during the two states of breath-holding.

In the light of all the evidence it would seem most probable that the experimental data presented for these supine subjects can most simply and satisfactorily be explained on the assumption that the loop and vectorial changes are, in most cases, the direct results of the anatomic displacements of the heart at the extremes of breath-holding.

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On the normalization of the electrical orientation of the heart and the representation of electrical axis by means of an axis map

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Routine clinical electrocardiography currently includes the interpretation of 12 individual leads by trained readers. A variety of other methods of recording the electrical activity of the heart have been suggested. In general, each method has some desirable and some undesirable characteristics for cardiac diagnosis. For example, the vectorcardiogram reflects the time phase of voltages in various electrocardiographic leads. This advantage is obtained, however, at the expense of an adequate representation of other temporal relations. In a similar fashion, other recording methods each have characteristics which make some information more accessible and some less accessible than does the routine electrocardiogram.

The purpose of this report is to describe a method of electrocardiographic recording and analysis which provides information that is not easily accessible in other records of cardiac electrical activity. Limited clinical experience with the method will also be reported.

The method employs a lead system which provides the three mutually perpendicular components of the heart vector. These voltages are passed through a device ("resolver") which alters the lead system so that the relative orientation of the heart with respect to the lead axes is changed. This process can be considered as an effective rotation of the heart within the body. The resolver is adjusted to "rotate" the heart, for both the QRS and T complexes, so that in each case the mean axis of the heart vector points toward the left side, and the plane of its motion is perpendicular to the long axis of the body. The original mean axis of the vector is then determined from the settings of the resolver knobs, and plotted on a map, along with the direction of motion of the vector. The voltages in the three new "normalized" leads are also recorded.

The information inherent in the three original electrocardiograms is thus separated into (1) a map which shows the mean axes of the QRS and T heart vectors, as

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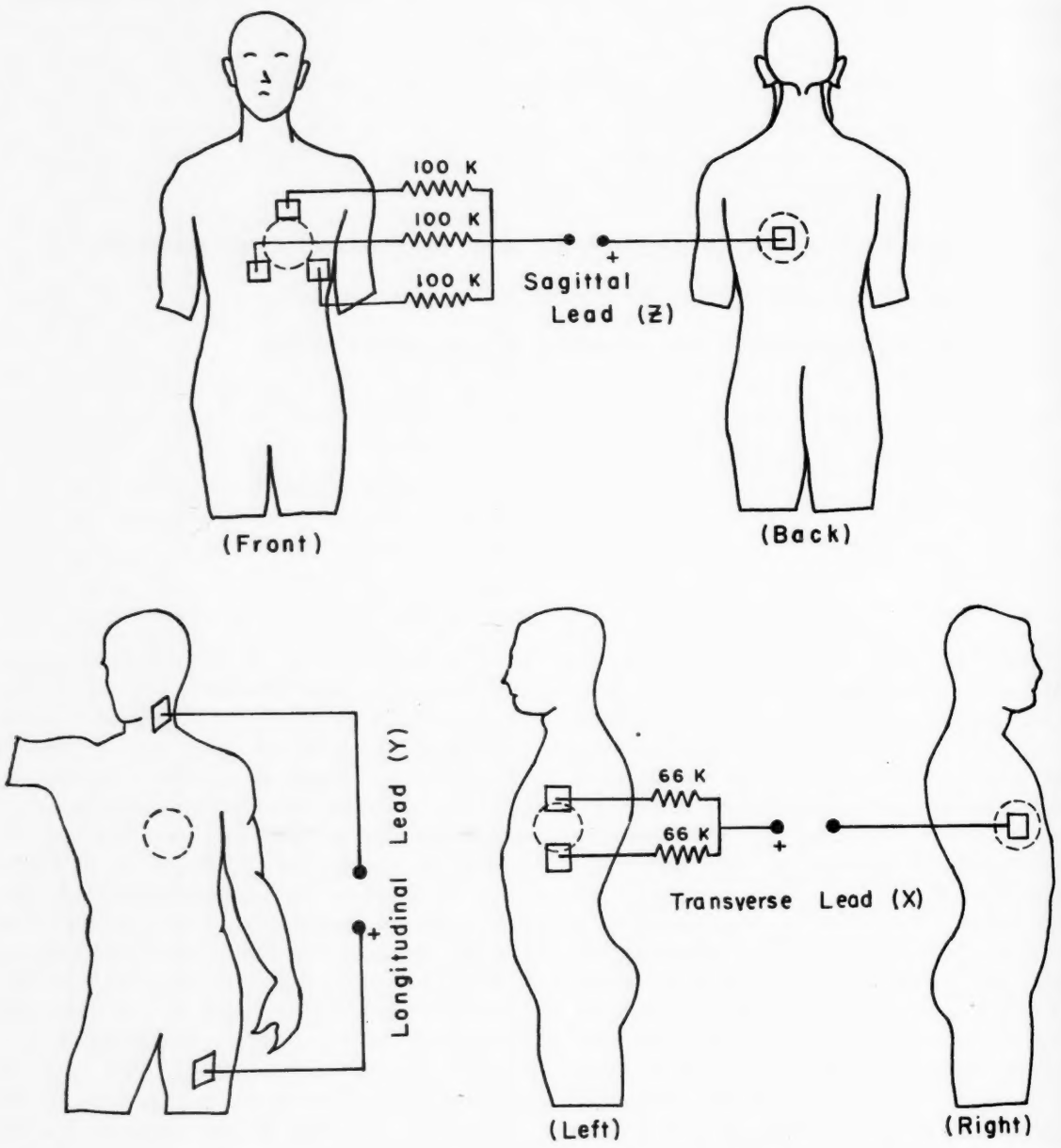

Fig. *1.* Sketch of the orthogonal lead system employed in these studies. For further details, see Reference 8.

well as the plane of their motion, (2) two sets of three "normalized" electrocardiograms which reveal at a glance the maximum magnitude of the heart vectors, the extent of their sweep, and their planarity. The latter records are free from the effects of variation of the position of the heart within the body.

The method is essentially an extension of the Einthoven concept of electrical axis into three dimensions, using relatively simple electronic instrumentation to determine the approximate mean axis of the QRS and the T. The method results in elimination of much of the normal variability of records from an orthogonal lead system.

Disadvantages of the method include the necessity for electronic equipment in addition to that employed in routine electrocardiography, and the time necessary to apply the technique.

Resolvers were first applied to electrocardiography by Schmitt.[1] More versatile equipment which permitted rotation about each of the three axes of an orthogonal

lead system has been employed by Rijlant[2] and by Koechlin,[3] and has been described by McFee and Parungao.[4] Clinical studies employing resolvers have also been reported by Milnor and associates.[5] Related but less flexible devices have been described by Brody[6] and by Pipberger.[7] Rijlant has employed a resolver to obtain electrocardiographic leads which are similar in some respects to those obtained in this study; however, the present study also includes a specific display of the lead-axis rotations necessary to obtain these leads.

Method of display and analysis

In the coordinate system used, the Y axis ("longitudinal") points toward the feet, the X axis ("transverse") toward the left side, and the Z axis ("sagittal") toward the back. The XYZ voltages have been obtained with the "axial" lead system (Fig. 1) described in a previous publication.[8] Other orthogonal lead systems can also be employed.

The operation of resolvers may be viewed either as a rotation of the lead system about a fixed heart, or as a rotation of the heart within a fixed lead system. Since rotations are relative, either view is equally valid. In this article the latter view is adopted.

With the method employed in these studies, the first resolver[4] rotation (θ) effectively turns the heart about the longitudinal (Y) axis.* If the θ knob is set to +90 degrees, a point formerly on the front of the heart next to the chest is moved around so that it is next to the left side. This angle can vary between plus and minus 180 degrees.

The second rotation (ϕ) turns the heart, already turned in effect about the longitudinal axis, about the sagittal axis (z). Setting the ϕ knob to +90 degrees moves a point adjacent to the left side to a location next to the neck. The range of ϕ variation is limited to $\pm$90 degrees.

The third and final rotation (δ) turns the heart, already rotated about the longitudinal and sagittal axes, about the transverse (x) axis. If the δ knob is set to +90 degrees, a point on the front of the heart next to the chest is moved downward to the area facing the feet. The δ angle can vary between plus and minus 180 degrees.

Through the use of a resolver, the heart can be effectively rotated into an orientation from which a more or less standard form of the electrocardiogram is obtained. This process is referred to here as "normalization." The specific procedure employed is the following one.

The "θ" knob is adjusted first so that the QRS deflection recorded from the Z output is equally positive and negative, with the principal deflection from the X output being positive. Adjustment of the "ϕ" knob is then carried out until the deflection from the Y output is also equiphasic. The "δ" knob is then turned until the Y output is as small as possible, with the initial deflection of the Z output negative. These steps are repeated to insure proper adjustment. The QRS complexes in the new XYZ output are then recorded. The entire procedure is repeated for the T wave.

One result of this procedure is a three-lead electrocardiogram in which the QRS in the Z lead is biphasic, that in the Y lead is small and triphasic or quadriphasic, and the major QRS deflection in the X lead is prominent and positive. A similar set of records in which the T waves have the same characteristics are also obtained.

Another result is two sets of three angles each representing the rotations about XYZ axes necessary to achieve the electrocardiographic patterns described.

To appreciate the geometric significance of the XYZ outputs and the angular rotations necessary to achieve these outputs, the heart may be visualized as surrounded by a spherical surface. Consider the sphere centered on the center of the heart and the "heart vector," by which cardiac electrical activity can be represented, located at this center. If extended, this vector would pierce the surface of the sphere, and the location of this point would define the direction of the vector. For example, if the vector was directed straight up, its extension would pierce the top of the sphere. The position of the point at which the vector pierces the sphere may be shown on a two-dimensional map of the surface of the sphere in the same manner that the position of a city is indicated on

*The order of rotations of the resolver has been changed from that specified in Reference 4.

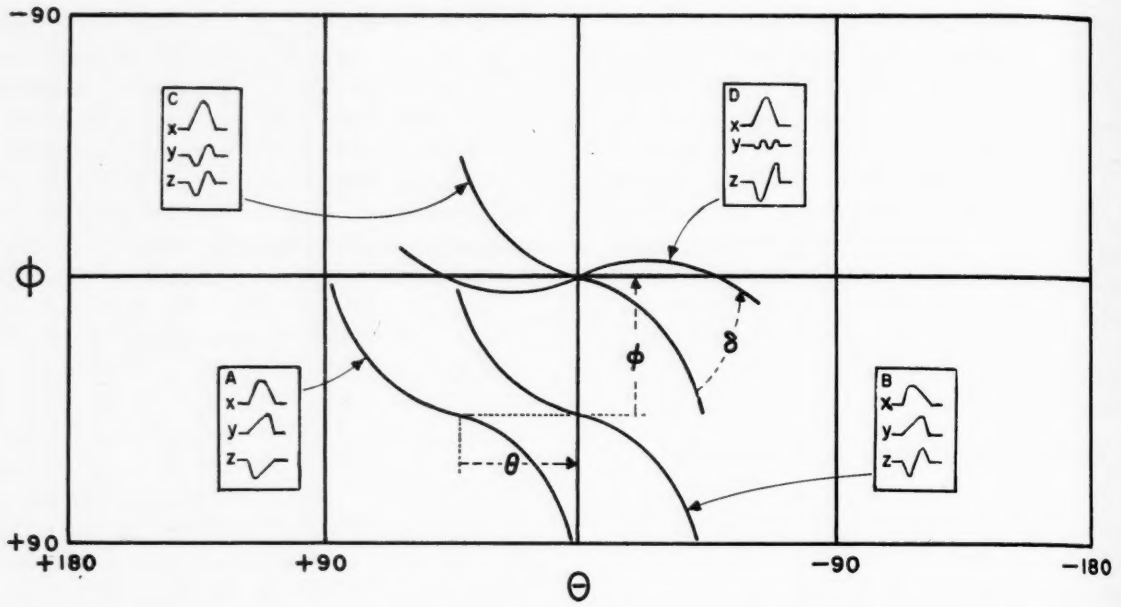

Fig. *2*. Diagrammatic map of the direction of the heart vector during the QRS complex, and the rotations necessary to achieve the normalized form of the complex. See text for detailed description of this figure.

a two-dimensional map of the surface of the world. The top of the map corresponds to that part of the sphere near the subject's head, and the bottom of the map corresponds to the part of the sphere near the feet. The center of the map is taken to represent that part of the sphere near the center of the left side, and its right and left edges correspond to the part of the sphere next to the line bisecting the right side. Lines corresponding to latitude and longitude on the sphere may also be shown on the map.

During the cardiac cycle, the point representing the changing direction of the heart vector defines an arc on the map, such as that labeled *A* in Fig. 2. This arc corresponds to the diagrammatic electrocardiographic lead voltages shown in the figure.

Rotation of the lead system about the Y axis, through an angle "θ," so that the output of the Z lead is equally positive and negative, moves the arc on the axis map to position *B* as shown in Fig. 2. A second rotation through the angle ϕ about the Z axis so that there is an equiphasic output from Y causes the arc on the axis map to move to position *C*. A final rotation about the X axis through the angle δ results in the smallest possible output of Y and moves the arc to position *D*. Changes in the appearance of the arc due to distortion by the map representation are not shown in Fig. 2.

Since in normal subjects the QRS and T axes are directed more or less toward the left side, the minimum rotation necessary to move the arc to this final position was obtained by taking the center of the map as the center of the left side of the body.

From the foregoing discussion the following points may be noted:

1. If the heart is considered to have been rotated in a fixed-electrode system, the cardiac vectors after normalization lie close to the horizontal plane, with their approximate mean axis pointing toward the center of the left side. This means that the maximal deflection occurs in the output of the normalized X lead.

2. The approximate original directions of the mean axes of QRS and T are indicated by the settings of the θ and ϕ knobs.* They may be plotted in the manner shown in Fig. 3. Such a diagram will be referred to here as an "axis map." The inclination of the plane of the motion of the heart vector can also be shown on the axis map, by

*A more precise normalization of the leads can be carried out by reducing to zero the area of the appropriate QRS and T deflections. This may be accomplished simply by electronic means since the adjustment is one which makes the integrated Y and Z outputs zero.

drawing an arrow on the map with an inclination equal to the setting of the δ knob. If δ is positive, the arrow points downward, and if negative, it points upward.

3. The peak deflection in the normalized X lead usually represents the maximal magnitude of the heart vector.

4. Deviations of the heart vector from a plane are reflected by the amplitude of deflections in the normalized Y lead. If no deflections occur in this lead, it indicates that the heart vector is confined to a single plane during the portion of the cardiac cycle being investigated.

5. The ratio of the amplitude of deflection in the normalized Z lead to that of the X lead reflects the range of the angular sweep of the heart vector during the portion of the cardiac cycle being studied.

6. The area of the spatial loop is approximately proportional to the product of the peak-to-peak amplitudes in the normalized leads X and Z. For an elliptical loop this area is $\left(\frac{\pi}{4}\right)$ (X peak to peak) (Z peak to peak). This area is equal to the magnitude of Burger's "polar" vector. After normalization, the polar vector points toward the head (considering the heart to be rotated in a fixed-electrode system). The direction of the polar vector before rotation can be determined from θ, ϕ, and δ, using either a set of equations or a special nomograph.

Clinical observations

The method described was applied to 29 normal subjects and 26 patients whose electrocardiograms showed a variety of ab-

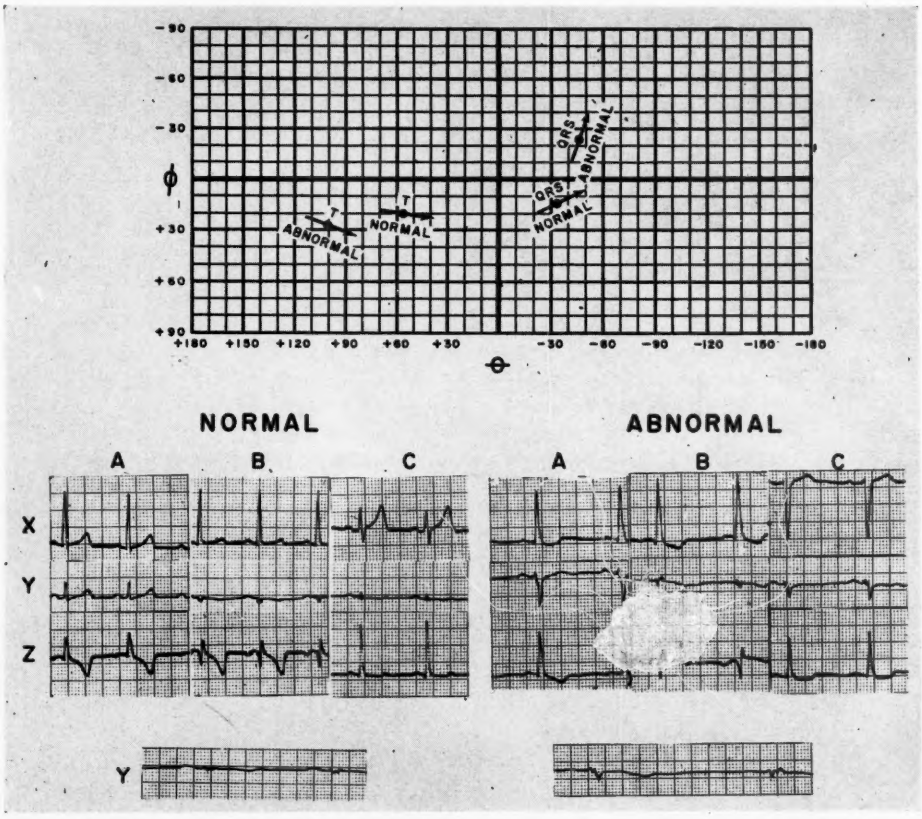

Fig. *3*. Representative normal and abnormal records. The XYZ leads from each subject are labeled *A*. Records of normalized QRS complexes are shown under *B*, and records of the normalized T waves, under *C*. Normalized QRS complexes in lead Y, recorded at a higher paper speed (50 mm./sec.), are also shown. The approximate mean directions of the heart vector during the QRS and T intervals are shown as black dots on the "axis map." These directions are obtained from the settings on the resolver dials after the electrocardiograms have been normalized. The inclination of the plane of motion of the heart vector is shown by the arrows through these dots.

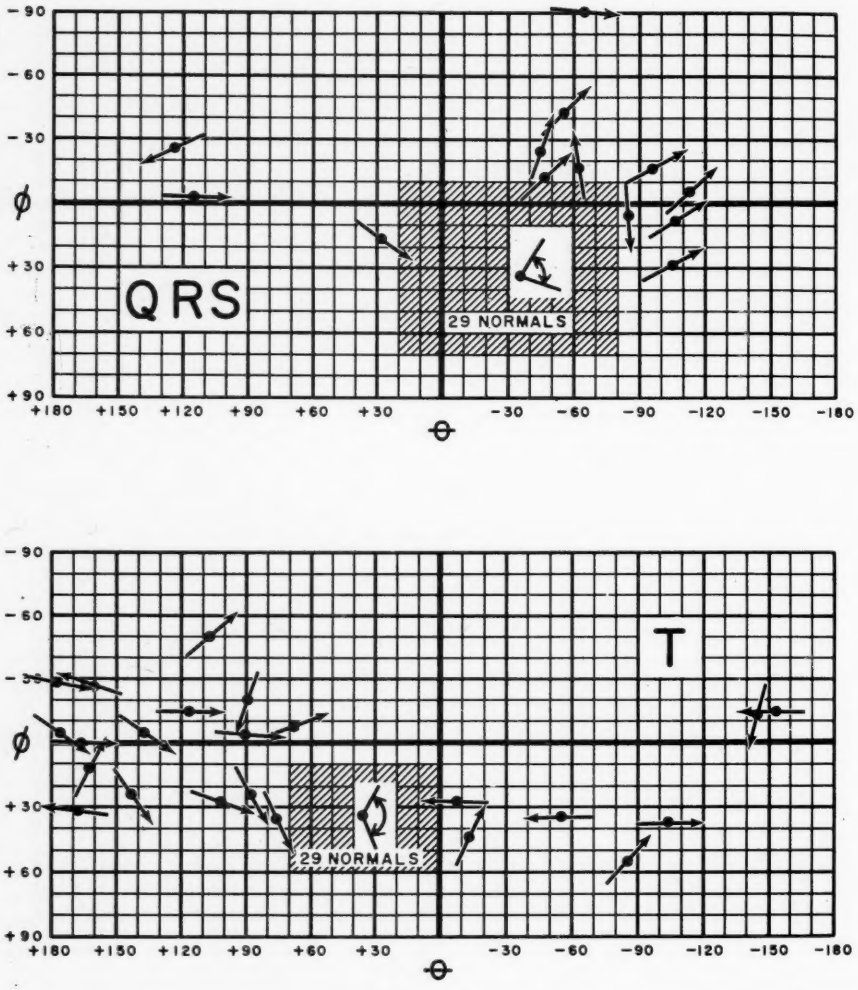

Fig. 4. These are axis maps of the approximate mean axes of the QRS complex and T wave as determined by the rotations necessary to achieve the normalized form of the electrocardiogram. Axes from 29 normal records fell within the shaded areas and had a range of inclination as shown by the insert in these areas. In 26 subjects whose conventional electrocardiograms were abnormal the approximate mean axis of either the QRS or the T or of both fell outside the normal range. In this figure all the approximate mean QRS and T axes which were located outside the normal area are shown.

normalities. The latter included nonspecific S-T-segment and T-wave abnormalities, evidence of myocardial infarction, left and right ventricular enlargement, and right and left bundle branch block.

Both normal and abnormal records exhibited variability in the amplitude of the heart vector as well as its angular sweep. Normalized records from some subjects with abnormal conventional electrocardiograms could not be differentiated from those of some normal subjects. It appeared, however, that there was greater variability in the entire group of normalized records from abnormal subjects. When quantitative normal standards have been established and individual abnormalities are investigated, it is possible that some of the parameters accessible in the normalized records will be clinically useful.

The axis maps provided an almost complete separation of the groups classified as normal and abnormal on the basis of the conventional electrocardiogram. All mean QRS and T axes from the normal group fell within the shaded areas shown in Fig. 4. Individual QRS and T axes from the patients whose conventional electrocardiograms were abnormal are also shown in this figure. Either the QRS or T axes,

or both axes, of all of these patients were located outside the area occupied by normal axes on the axis map. These findings indicate that much of the electrocardiographic information on which a separation into normal and abnormal groups is made by routine interpretation is reflected by the mean axis of QRS and/or T waves.

Since a variety of electrocardiographic abnormalities were represented in the abnormal group, and there were only small numbers of each specific abnormality, a definition of the characteristics of individual abnormalities in the axis maps and the resolved leads was not attempted. For this type of study, larger numbers of records of individual abnormalities will be necessary. It is not unlikely that clinically useful correlations will eventually be found between some of these abnormalities and unusual characteristics of the amplitude, sweep, and planarity of the heart vector, as shown by the normalized electrocardiograms.

Discussion

The method of analysis and display described reduces the variability of a set of orthogonal leads to a minimum. When the normalized XYZ records from patients with abnormal cardiac electrical activity fall within the range of variability of "normalized" records from normal subjects, the abnormalities are reflected by the axis map. Quantitative description of the range of normal variability in the axis maps is so simple that abnormalities reflected in the maps may be readily recognized.

The major finding of the present study was that normal records and a group of miscellaneous electrocardiographic abnormalities could be separated by the axis maps. This constitutes an approach to machine interpretation of the electrocardiogram, since the only element of interpretation in the technique was that of matching Y and Z leads to a predetermined pattern by adjusting the resolver knobs.

The display of normalized XYZ leads also has several other characteristics of interest. The degree of nonplanarity of cardiac electrical events is presented in quantitative terms. The approximate magnitude and orientation of the polar vector, the angular sweep of the heart vector, and the maximal magnitude of the QRS and T vectors may be easily determined from the normalized leads. Any or all of these parameters may have clinical usefulness in the recognition of specific abnormalities of the electrical activity of the heart. Further study of larger numbers of records will be necessary to evaluate this possibility.

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Compromise in vectorcardiography
Displacement of electrodes as a means of adapting one lead system to another

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The variety of systems of vectorcardiography, and the discrepancies existing between various systems, even among those with a well-founded physical basis, have impeded full acceptance of vectorcardiography for clinical use. Standardization is urgently needed, but cannot be realized yet at the present time.

One thing is certain: all systems without rational physical foundation must be abandoned. If two systems differ, although both have a sound physical foundation, a step toward standardization may be taken if a compromise between the two systems can be found.[1]

A lead system is characterized, first, by the choice of the electrode positions, and, second, by the manner in which the voltages are combined with the use of coefficients (or lead vectors). Thus, there are two methods of making a compromise between two systems, viz., by proper change of the coefficients or by displacement of the electrodes. Since instruments which allow a free choice of the coefficients are not generally used, we chose to investigate the second method.

The systems investigated were Schmitt's SVEC-II[2] and our B_1W_4''[3,4] which we will indicate here by the letters S and B, respectively. Inasmuch as we have only recently become aware that our system has never been described explicitly, we wish to present its technical particulars here. The following electrode positions are used: right arm (R), left arm (L), left leg (F), chest, a mid-sternal electrode placed at the level of the axillae (B) and back, the dorsal electrode of Wilson's tetrahedron, 2 cm. to the left of the seventh thoracic vertebra (W).

Since the number of independent combinations of electrodes amounts to one less than the number of electrodes, 4 leads are obtained from these 5 positions. The leads are so chosen that only one electrode (R) is combined alternatively with each of the others, yielding the leads LR, FR, BR, WR. The lateral, longitudinal, and sagittal components* of the vector are obtained by combining the leads with one another and assigning them with coefficients determined by model experiments.

$$X = 56LR + 16FR + 4BR - 9WR$$
$$Y = -9LR + 26FR - 3BR + 7WR$$
$$Z = 9LR - 27FR - 20BR + 40WR$$

(LR = potential of L − potential of R, etc.)

It is evident that any alteration in the positioning of even one electrode in this system would result in a change of the value of all 3 components of the vector.

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*The American notation has been followed, in which the axes are chosen as follows: X = right −, left +; Y = cranial −, caudal +; Z = ventral −, dorsal +.

This, in turn, would require new values for the coefficients. In the S-system, each component of the vector is determined by one single lead. Consequently, we have chosen to adapt the S-system to the B-system and not the reverse. This does not mean, however, that we attribute the difference of these two systems to an error in S only.

Method and material

In the Schmitt system there is no mention of a scale, so that we have chosen the sensitivity in such a manner that the sizes of the loops in the S and B systems were, on the average, approximately equal. The frontal and horizontal projections in each system were photographed simultaneously.

The agreement between the frontal projections of the two systems is satisfactory; the main discrepancy is in the horizontal projection, and is the consequence of the uncertainty in the determination of the sagittal component of the heart vector, caused by the relatively small dimensions of the human thorax in the sagittal direction.

It appeared that in the S-system a footward loop generally is directed more posteriorly than in the B-system. This was expressed previously[3] in an analytical form by the relation:

$$Z_S = -0.2\ X_B + 0.6\ Y_B + 0.9\ Z_B$$

in which Z_S is the sagittal component of the vector in the S-system, and X_B, Y_B, and Z_B are the components in the B-system. Because of the contribution of the Y-term, which is positive for points of the vector loop below the zero point, Z_S will become proportionately greater than Z_B at points which are increasingly distant from the zero point, moving in a caudal direction.

The sagittal component in the S-system is exclusively determined by, and proportional to, the voltage between its dorsal and precordial electrodes. Consequently, the desired change in this component might be attempted by shifting these two electrodes. The anatomic axis connecting these electrodes changes, therefore, in position; we choose to call this axis the "pick-off" axis. If the dorsal electrode is displaced cranially and the precordial electrode caudally, an inclination of the sagittal pick-off axis is effected. This will bring about a decrease in the magnitude of the projection on the axis of a caudo-posteriorly directed vector, and an increase in the case of a caudo-anteriorly directed vector. The net result would be a rotation of the vector loop in the ventral direction, over a certain angle (see Fig. 1). This reasoning would only be fully justified if image space and anatomic space were considered to be identical, which is certainly not true. Preliminary investigations, however, have supported the above-mentioned displacement of electrodes; the distance was empirically established at 6 cm. for each electrode.

Our material comprised 64 normal individuals and 86 cardiac patients. Comparisons were made by three observers independently, by grading the agreement between the horizontal projections of the loops according to a scale ranging from 0 to 10. A score of 10 indicated as perfect an agreement as could be expected to exist within one system between different heart beats of the same subject.[3-5] An example of the improvement in agreement between systems B and S is shown in Fig. 2.

Results and conclusions

From the group material the average of the scores obtained from the comparison

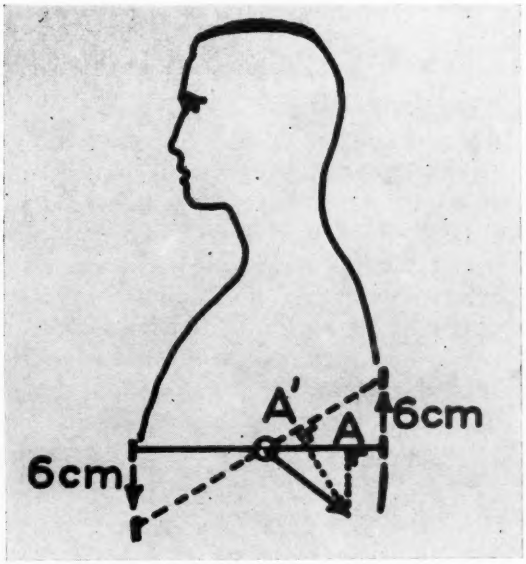

Fig. 1. *OA* represents the projection of the heart vector on the pick-off axis before, and *OA'* after, displacement of the electrodes. It can readily be seen that OA' < OA for posteriorly directed vectors.

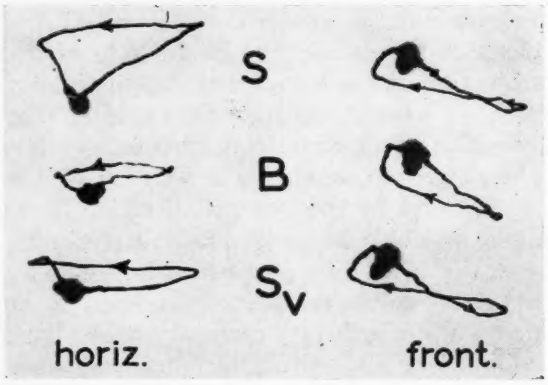

Fig. 2. S_V, the loop obtained after displacement of the electrodes, shows a better resemblance to *B* in the horizontal projection than does *S*.

between B and the original S and its variant S_V, respectively, revealed a value of 6.0 ± 0.12 for B-S and 6.5 ± 0.12 for B-S_V. The average of the individual differences between B-S and B-S_V was 0.5 ± 0.07. This difference is statistically significant, but the improvement is hardly large enough to render the method worth while for practical use in its present form. The failure of this result to fulfill our expectations may be attributed to: (1) the application of a rotation instead of a shear, which would be required considering the above-mentioned formula for Z_S; (2) the assumption that the discrepancies between S and B are due to a difference in the sagittal components only and can be remedied by changing these components only; (3) the assumption that image space and anatomic space are identical.

Therefore, we have abandoned this method and have turned our attention to the procedure of changing the coefficients.

Summary

An attempt was made to improve the agreement between the Schmitt SVEC-II and the Burger B_1W_4'' systems by shifting the ventral and dorsal electrodes of the SVEC-II system caudally and cranially, respectively. Although a statistically significant improvement in agreement was obtained, it hardly warrants practical use of the procedure.

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Effect of tilting on RK time in normal subjects and in patients with heart disease

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Experiments in our laboratories[1] have demonstrated that the time lag from a reference point on the QRS complex of the electrocardiogram (Q or R) to the onset of aortic ejection (E) becomes shorter as the stroke output increases. The velocity of arterial transmission of the pulse wave is not affected by these changes in output. Thus, variations in stroke output may affect the arrival time of the pulse wave at the brachial artery.

During a given beat, the arterial sound begins as the pulse pressure rises to and then exceeds the cuff pressure. We have utilized the arterial sounds to represent the time of arrival of the pulse wave at a given cuff pressure. A reference electrocardiogram recorded with the sound permits measurement of the electromechanical lag. The sensitivity of this method is shown by the fact that the time from the midpoint of the upstroke of the R wave of the electrocardiogram to the onset of the arterial sounds of Korotkoff (K) at a given cuff pressure level is shortened consistently by procedures which increase stroke output, such as general exercise or the administration of epinephrine or norepinephrine.[2,3] The possibility was therefore suggested that RK time may provide a clinical assay of changes in stroke volume.

Postural changes are known to affect the venous return and thereby to modify the stroke volume. The purpose of the present study was to evaluate the cardiodynamic effects on the RK time induced by postural changes in normal subjects and in patients with congestive heart failure. An electronic instrument designed and constructed in this laboratory was used to record the arrival time of the arterial sounds at various arterial pressures.[4]

Materials and methods

Studies were carried out on 14 normal subjects and 17 patients. The brachial arterial sounds during routine measurement of blood pressure were picked up by a microphone which was held firmly to the skin by a suction cup. The arterial vibrations were inscribed on a cathode-ray oscilloscope; each horizontal sweep was triggered at a selected isovoltage level near the peak of the R wave of the electrocardiogram. The R wave was used since this large wave was more effective in triggering

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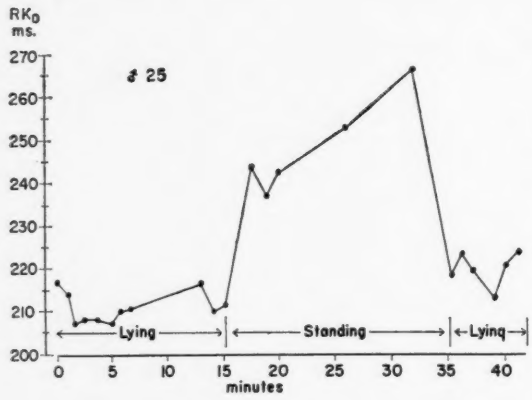

Fig. *1.* Data obtained in successive readings on a 25-year-old healthy male. Vertical scale gives the time from onset of R wave to onset of arterial sound when cuff pressure is at diastolic pressure levels (RK_D). Horizontal scale is time in minutes. Each dot represents a single measurement. The first 11 dots represent a normal variation of about ± 5 msec. around an average of 212 msec. The next 4 dots represent the change while the subject is standing passively; RK_D is prolonged at once to 235 msec. and increases gradually to 265 msec. Immediately on passive return of the subject to the lying position, the RK_D shortens to about 220 msec. Discussed in text.

the sweep than the smaller Q wave. Tests showed that the difference between the onset of the Q and the point of triggering on the R wave was about 30 milliseconds (msec.). In each case this value was determined from the electrocardiogram.

The tracing was photographed with a Polaroid camera, and the interval from the upstroke of the R wave of the electrocardiogram to the onset of the sound was measured on the finished record. Time and calibration pulses introduced into the record permitted measurement of onset of the sounds to within 5 msec. By varying the delay time between the activation of the R-wave triggering circuit and the onset of the sweep, we were able to make several recordings on each film.

Four to 10 records were obtained in each experiment as the patient lay supine on a tilt table. A similar series was made after the patient was passively changed to the 75-degree upright position and again after return to the horizontal.

Results

1. Reclining subjects at rest. In 11 normal subjects the average RK time at diastolic pressure levels (RK_D time) was 207 msec., ranging from 191 to 242 msec., in accord with previous findings.[2]

In 8 patients with previous or present congestive failure, the RK_D times averaged 198 msec., varying from 146 to 236 msec. Thus, RK_D did not assist in differentiating the patients with failure from the normal subjects.

2. Effect of postural change.

A. NORMAL SUBJECTS. Fig. 1 shows a serial record of RK_D times during postural changes in a normal subject. When the subject was in the supine position, RK_D varied from 207 to 217 msec., with an average of 211 msec. After the subject was moved into the standing position, the RK_D was significantly prolonged by 30 msec. or more. Return of the subject to the supine position shortened RK_D to approximately the control level (Table I). Similar results were obtained in all of 14 normal subjects tested (Fig. 2).

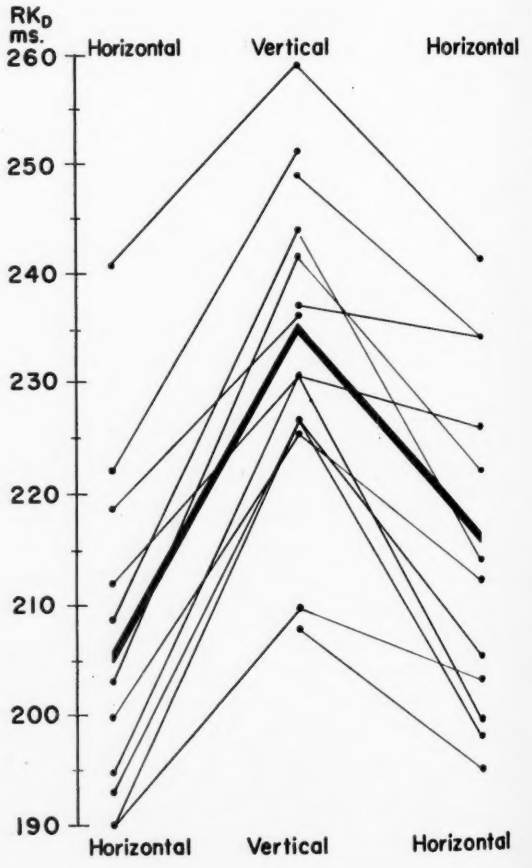

Fig. *2.* Averages of data on effect of posture in each normal subject (*light lines*) and in the entire group (*heavy line*) as the position was changed. The average increase in RK_D time was 30 msec., with incomplete recovery on return to the horizontal.

Table I. *Average changes in* RK_D *time*

Postural change	*14 Normal subjects*	*8 Patients with congestive heart failure*
Horizontal to vertical	+35 msec.	+6 msec.
Vertical to horizontal	−19 msec.	+12 msec.

+Prolongation. − Shortening.

B. PATIENTS WITH PREVIOUS OR PRESENT CONGESTIVE HEART FAILURE. In the cardiac patient the prolongation of the RK_D time when he was standing, and the shortening after he was returned to the horizontal position were less marked than in the normal subject (Table I). In some tests, RK_D in the cardiac patients showed a reversal of the normal response; RK_D was slightly shortened after the patient had assumed the upright position and slightly prolonged after he was returned to the horizontal position (Fig. 3).

3. Effect of an antigravity G-suit. To eliminate the gravitational tendency of blood to pool during passive standing, postural tests were carried out in 5 normal subjects wearing an Air Force antigravity suit inflated to 260 mm. Hg (Table II). The antigravity suit consisted of nylon trousers arranged so that air bladders compressed the calves, thighs, and abdomen of the subject. Fig. 4 shows that while the suit was inflated, the RK_D changed only slightly when the subject assumed the standing position. When the air pressure in the suit was then dropped to atmospheric levels, a significant prolongation of the RK_D time by as much as 47 msec. occurred.

In the present experiments the diastolic pressure remained relatively constant during the postural changes; it rose an average of 2 mm. Hg when the subject was standing, and fell an average of 3 mm. Hg when he resumed the supine position. These slight changes in diastolic pressure did not correlate with the RK_D time.

Discussion

The normal heart responds to an increase or decrease in venous return with similar variations in the stroke output. The heart in failure, on the other hand, may be unable to maintain this performance.

Normal subjects showed a significant prolongation of RK_D time when they assumed the erect position, and a shortening of this time when they returned to the horizontal position. It is generally appreciated that change of position shifts a significant volume of blood to the dependent portions of the body. The transitory reduction in the venous return to the heart on assumption of the upright position can thus be expected to produce a fall in cardiac stroke and minute output.[5-9] The compensatory vasoconstriction which maintains the systemic blood pressure cannot affect this deviation of blood volume to the venous system. Sustained inflation of the antigravity suit counterbalances the gravitational tendency for venous pooling and thereby reduces the effects of assumption of the upright position.[10] Our data, showing a prolongation of the RK_D time on passive standing, which is inhibited by a G-suit,

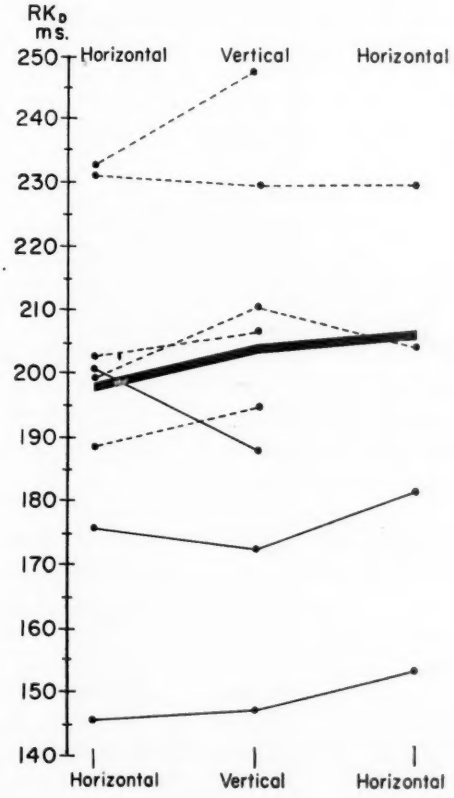

Fig. 3. Effect of changes in posture on RK_D in patients with heart failure. Conventions as in Fig. 2. Each dashed line represents average data on a patient with previous heart failure. Each solid line represents average data on a patient in congestive failure. The heavy bar is the average of the entire series.

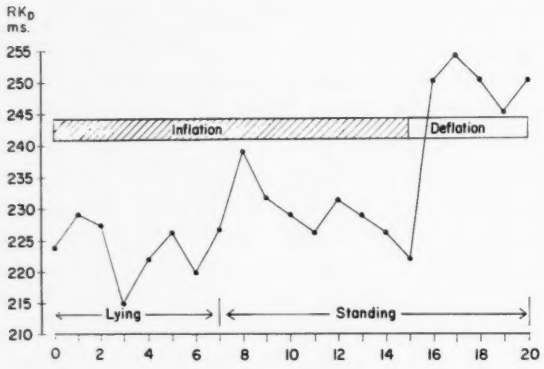

Fig. 4. Effect of G-suit on postural changes in RK_D time. The number of the trial is given in the horizontal scale. Inflation prevented the expected prolongation of RK_D time when the subject was moved to the upright position. When the G-suit was deflated, the RK_D time was prolonged by about 30 msec. Discussed in text.

are consistent with the expected changes in stroke volume.

RK_D time may be subdivided into two functional intervals: (1) the RE interval, from R of the electrocardiogram to the onset of ejection (E); and (2) the EK interval, i.e., the time for transmission of the pulse wave from the aortic valve to the point of production of the arterial sounds.

Since the time for transmission of the pulse wave at a given diastolic pressure appears to be unaffected by changes in position of the body, the variations of the RK_D time which we observed must be considered as being due to changes in the pre-ejection (RE) time. Recent studies on animals in this laboratory[1] have demonstrated that at constant diastolic pressure the RE time shortens as the stroke volume is increased, whereas the pulse wave velocity (EK) remains unchanged. It may then be suggested that variations in the RK_D time during specific interventions, such as tilting, may be utilized clinically to appraise changes in stroke volume. A shortening of RK_D may thus indicate an increase in stroke volume, whereas prolongation may represent a decrease in stroke volume.

The stroke output of patients with congestive heart failure remains relatively unchanged despite exercise or the intravenous infusion of fluids.[11-13] The diminished response of the RE time to the postural change may reflect a limitation in stroke output in cardiac patients. Wiggers' intraventricular pressure curves[14] demonstrated that after infusion of saline the isometric pressure upstroke became steeper and the isometric contraction period was shortened. After excessive infusion and the development of cardiac "failure," as evidenced by a diminishing contractile power, the steepness of the upstroke decreased and the isometric contraction time was prolonged.

We may assume that the increase in venous return after the subject has taken the horizontal position, and the decrease when he is standing, should similarly affect the steepness and duration of the rise in intraventricular pressure. However, this effect was not seen in the patients with failure. Dysfunction of the myocardium may thus be reflected in the patterns of modification of the RK_D time after postural changes.

Table II. *Effect of G-suit on postural change**

Age (*yr.*)	*Without G-suit*			*With G-suit*		
	Lying (*msec.*)	*Standing* (*msec.*)	*Difference* (*msec.*)	*Lying* (*msec.*)	*Standing* (*msec.*)	*Difference* (*msec.*)
21	220	237	17	231	230	−1
44	191	211	20	204	204	0
27	201	227	26	162	168	6
24	204	247	43	224	229	5
39	191	228	37	224	218	−6
Average	201	230	29	209	210	1

*All subjects were males.

These data suggest that recordings of arrival time of the pulse wave during a given cardiac cycle may provide significant information concerning cardiovascular status. The simplicity of our method permits recurrent clinical assays of changes in cardiac function during physiologic and therapeutic studies.

Summary

The time from onset of the R wave of the electrocardiogram to the registration of the arterial compression sound of Korotkoff at diastolic pressure level (RK_D time) was measured before and after passive changes in posture. In normal subjects the RK_D time was significantly prolonged after they assumed the upright position and shortened to control values when they returned to the horizontal position. These effects were diminished by compression of the calves, thighs, and abdomen of the subject with an antigravity suit.

In patients with previous or present congestive heart failure the response of the RK_D time to the changes in posture was significantly reduced or was opposite to that seen in normal subjects.

These data may be interpreted to suggest that in normal subjects with a relatively constant level of diastolic pressure, RK_D time varies inversely with the stroke volume. This relationship is eliminated in patients with congestive failure. The simplicity of the method permits the study of responses to experimental or therapeutic procedures.

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Case report

Anomalous coronary artery connecting with the right ventricle associated with pulmonary stenosis and atrial septal defect

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Congenital abnormalities of the coronary arterial system are becoming of greater importance, since surgical treatment is possible. Preoperative diagnosis is therefore of paramount importance. Diagnosis should include the type of abnormality, the presence of associated defects, and the type of hemodynamic disturbance produced. One group of coronary arterial malformations is of purely academic interest since no functional disorders arise from them; quite often they are found at autopsy. Such is the case with a single coronary artery, both coronary arteries arising from the same aortic sinus, some of the distribution abnormalities, etc. There is another group of malformations the importance of which is evident inasmuch as they represent abnormal left-to-right shunts. Such is the abnormal connection of one coronary artery with one of the cardiac chambers (right auricle, coronary sinus, right ventricle) or with the pulmonary artery, thus establishing a shunt between systemic and pulmonary circuits. Sometimes the connection is made with the left cardiac chambers, giving rise to an arterial-systemic shunt. Edwards and Burchell[1] reviewed the subject of the anomalous origin of the coronary artery from the pulmonary artery and suggested the possibility of ligating the abnormal coronary vessel, since hemodynamically this condition acts as an arteriovenous fistula. Six patients with such a condition have been operated upon to date.[2,3,3a]

On occasion, combinations of coronary arterial abnormalities lead to complex malformations which are difficult to diagnose and treat. The case which will be presented, illustrates this situation inasmuch as there was a single coronary artery with abnormal distribution and abnormal situation, one the branches of which connected with the cavity of the right ventricle. This condition was associated with a trilogy of Fallot (atrial septal defect plus pulmonary valvular stenosis).

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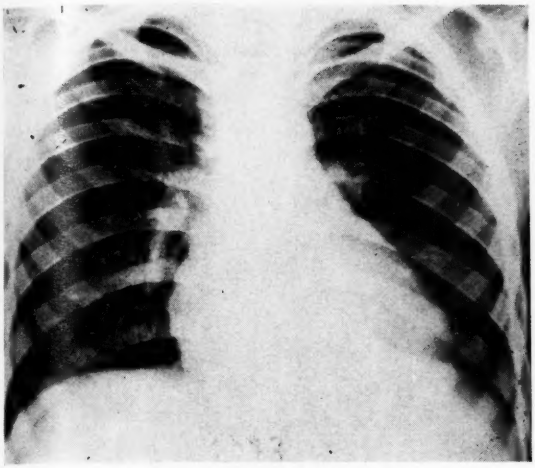

Fig. *1A*. Frontal view. Slight cardiomegaly. Straight middle segment and normal hilar vessels. Peripheral vascularity is decreased.

Description of case

L.R.L. was a 6-year-old boy who had been born of an uncomplicated pregnancy and normal delivery. A congenital heart condition had been recognized when he was 1 month of age. He remained asymptomatic until he was 3 years old, at which time easy fatigability was noticed. Cyanosis was present when he was examined, but it had not been apparent to the mother, for which reason the time of its appearance remains unknown. Physical examination in December, 1959, disclosed a poorly developed cyanotic child who was 108 centimeters in height and weighed 17.700 kilograms. Clubbing of the fingers and toes was evident. The apex of the heart was felt at the fifth left intercostal space in the mid-clavicular line. A systolic thrill was felt at the third and fourth left intercostal spaces. At this site there was a harsh holosystolic murmur, Grade 3+, which extended toward the base, especially under the left clavicle. There was a soft "superficial" diastolic murmur at the mid-precordial area, extending somewhat to the apex. The second pulmonary sound was of decreased intensity and "pure."

On x-ray examination, the heart in the frontal view (Fig. 1*A*) appeared to be slightly increased in size. The pulmonary segment was straight, the hilar vessels were normal, and the periphery of the lungs were overly transparent.

The electrocardiogram (Fig. 1*B*) suggested right auricular enlargement and right ventricular hypertrophy.

The child was thought to have a tetralogy of Fallot associated with some other anomaly responsible for the diastolic murmur. It was suspected that a coronary vessel connected with one of the right cardiac chambers or that there might be an added aortic regurgitation.

A conventional catheterization demonstrated an atrial septal defect with a right-to-left shunt (Table I). There was a large gradient of 91 mm. Hg across the pulmonary valve, and the graphic registration of the pressures indicated a valvular type of pulmonic stenosis. The difference in pressure between the ventricles substantiated the idea of an intact ventricular septum.

An angiocardiogram (Fig. 2) was made with a No. 8 Lehman catheter injecting 32 c.c. of 70 per cent Reopak directly into the right ventricle. Plates were taken in the posteroanterior and left lateral views. The right ventricle was seen to have a hypertrophic wall, i.e., marked trabeculation and increased thickness of the crista supraventricularis. A dome-shaped valve was visualized, and the eccentric jet which emerged from it was readily visible during systole. Throughout the first second a round-shaped image (frontal view) began to appear near the apex of the right ventricle; this image was continued by a tortuous path, a vessel of irregular caliber, which ascended parallel to the outflow tract of the right ventricle (Fig. 2*A*). In the lateral plane (Fig. 2*B*) this structure could be seen to lie on the anterior border of the cardiac contour. The levoangiocardiogram (Fig. 2*C*) showed that this vessel emerged from the aorta immediately above the level of the aortic valve. We concluded that this was an anomalous connection of a coronary artery with the right ventricle associated with a trilogy of Fallot.

An interesting feature of this case was that during systole the right ventricle pumped blood through the anomalous coronary vessel into the aorta, and during diastole, blood regurgitated from the aorta into the right ventricle.

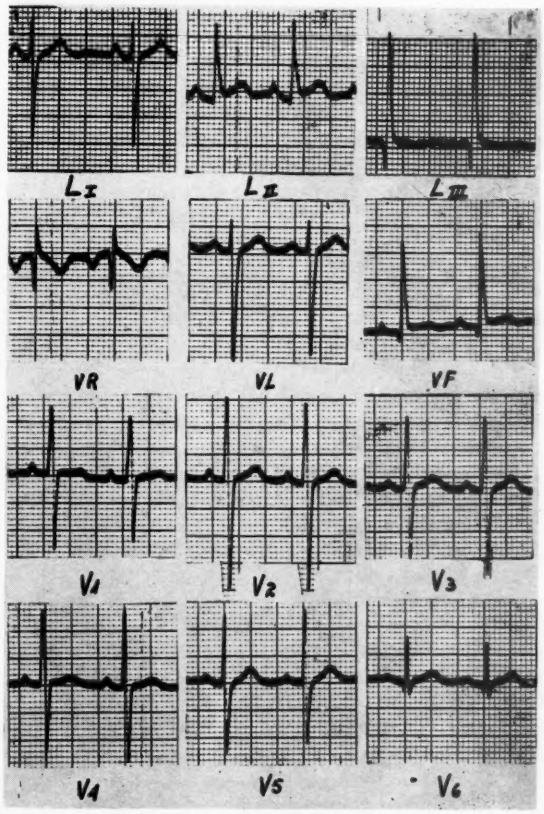

Fig. *1B*. The electrocardiogram shows right axis deviation and RS complexes with a positive T wave in Lead V_1. The tracing is suggestive of right ventricular enlargement.

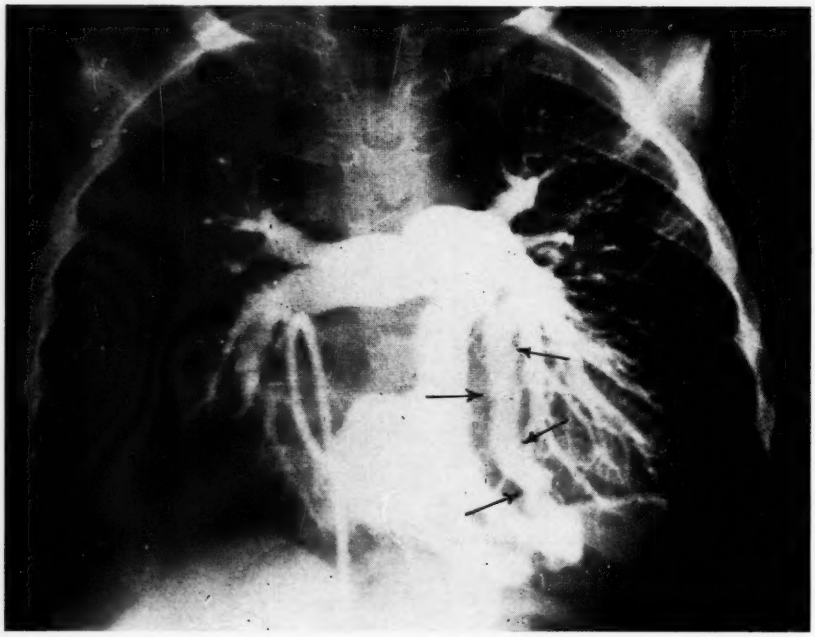

Fig. *2A*. Angiocardiogram in the frontal plane. The inflow tract of the right ventricle and the pulmonary artery are filled with opaque substance. The arrows point out the path of the abnormal coronary artery.

The patient underwent operation in May, 1960. When the pericardium was opened, the surgeon visualized the dilated and tortuous coronary vessel which connected with the right ventricle, entering the ventricular cavity at the lower third of its anterior aspect, where it formed an aneurysmal dilatation. A thrill was felt over the entire length of the vessel. A clamp was placed on this coronary artery about 4 cm. from its origin at the aorta. Since no electrocardiographic abnormalities appeared, the vessel was interrupted. The valvular pulmonic stenosis was then treated by means of the open-heart technique. A markedly stenosed valve was found. The crista supraventricularis was partially resected in order to widen the infundibulum. When the chest was closed, cardiac standstill occurred. The heart was massaged and it recovered, but within an hour a second standstill took place and the heart never recovered again despite resuscitative measures.

*Autopsy report.** The heart weighed 115 grams. The anterior aspect of the right ventricle showed a ventriculotomy incision which was about 4 cm. in length. The anterior descending coronary artery was sectioned in its middle part, 4 cm. distant from its origin. An atrial septal defect was seen when the heart was opened. The right ventricle showed the partially resected crista supraventricularis. Its cavity was moderately dilated and its wall was hypertrophic. The pulmonary sigmoid valve cusps were thickened, and they showed a surgical disruption (Fig. 3*A*). A single coronary artery was found emerging from the right anterior sinus of Valsalva of the aortic valve (Fig. 3*B*). The ostium to this vessel measured 0.6 cm. in diameter. The path followed by the vessel was directed downward, forward, and to the left. It gave off some branches about 3 cm. from its origin. It proceeded along the anterior interventricular sulcus, showing a changing caliber which varied between 15 and 20 mm. in circumference. It opened into the right ventricular cavity at the level of the inferior and anterior third of the interventricular septum, where it had made a tunnel of irregular shape, lined with endothelium, and showed numerous small holes of different sizes, corresponding to many finer vessels. The opening was located at the trabecular zone.

Injection of the coronary network through the ostium of the single coronary artery with the technique described by Schlesinger (modified by Reiner and associates[4]) demonstrated the filling of the artery, of two large branches, and of several smaller twigs which spread through both ventricles in the fashion of an extensive collateral network (Fig. 4*A*). The different branches of the abnormal coronary artery arose from the main vessel at very obtuse angles in the distal sense (Fig. 4*B*), in contrast with the normal pattern.

*The autopsy was performed by Dr. E. Perez.

Discussion

Abnormal connection between a coronary artery and one of the cardiac chambers is an unusual malformation; only 52 instances have been reported to date in the literature. In 16 of these, operation was successfully carried out,[5-14] and in 2 (Bosher and associates' case[15] and ours), death occurred postoperatively. In only 3 of the cases in which operation was performed were there associated malforma-

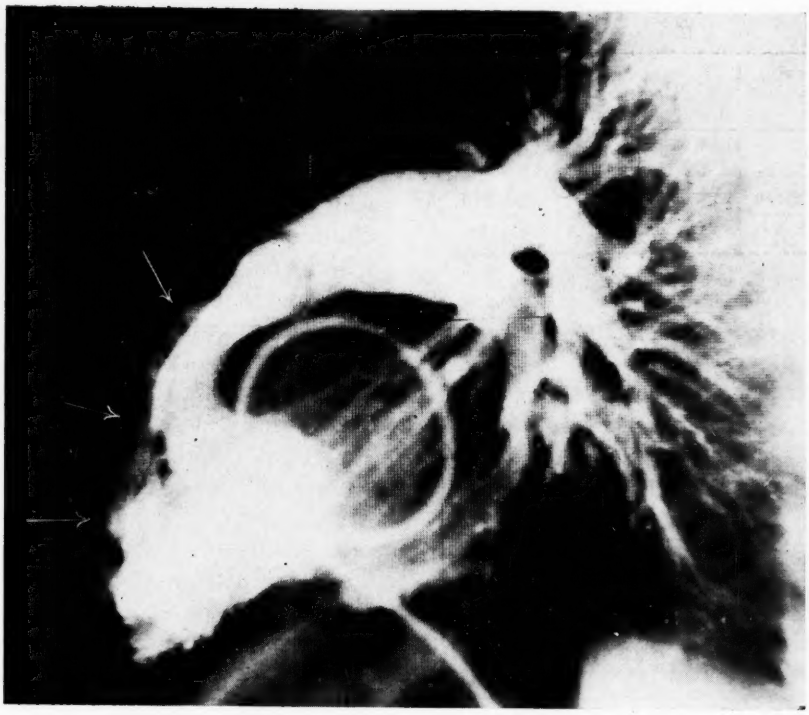

Fig. *2B.* In the lateral plane the prominence of the crista supraventricularis is visible. Notice the dome-shaped stenotic pulmonary valve. There is slight poststenotic dilatation of the pulmonary artery. Notice the path of the anomalous coronary artery at the anterior border of the cardiac contour pointed out by the arrows.

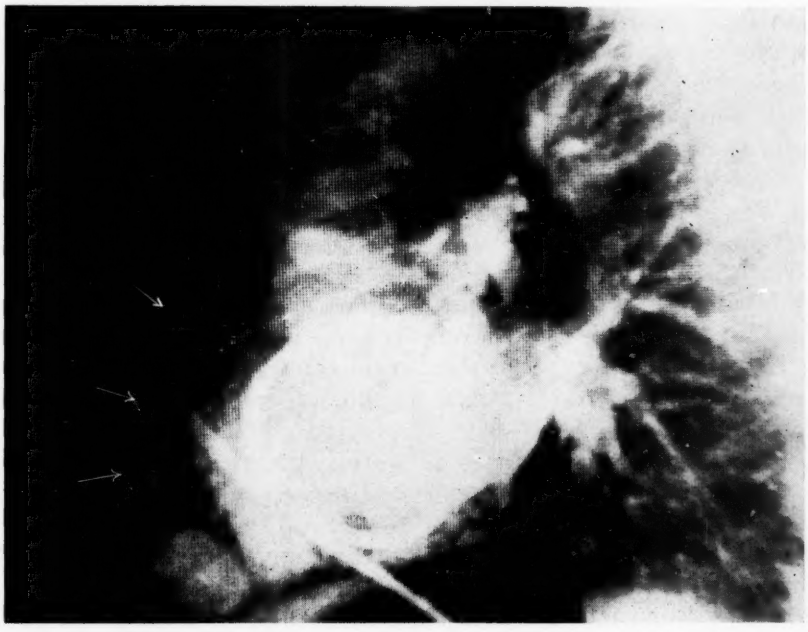

Fig. *2C.* The levoangiocardiogram shows the abnormal coronary vessel (pointed out by the arrows) arising from the aorta and reopacifying the right ventricle after an anterior course.

Table I

	Gas analysis		*Pressures (mm. Hg)*		
	Vol. (%)	*Saturation (%)*	*Systolic*	*Diastolic*	*Mean*
IVC	12.56	60	—	—	—
RA	12.66	61	—	—	2.5
RV	11.40	55	105	−7/0	52.5
PA	9.12	44	14	—	7.5
WP	—	—	—	—	2.5
LA	14.52	70	—	—	2.5
LV	15.50	72	77.5	2.5/5	37.5
FA	15.56	76	—	—	—

Oxygen capacity: 20.49 vol. %
Hemoglobin: 15.29 Gm. %
Oxygen consumption: 173 c.c./min.
Pulmonary flow: 1.374 L./min.
Systemic flow: 5.760 L./min.
Right-to-left shunt: 3.386 L./min.

IVC: Inferior vena cava. RA: Right auricle. RV: Right ventricle. PA: Pulmonary artery. WP: Wedge pressure. LA: Left auricle. LV: Left ventricle. FA: Femoral artery.

tions: both the case of Bosher[15] and that of Sondergaard[8] were complicated by patent ductus arteriosus, and ours was complicated by trilogy of Fallot.

Up to 1950, only 42 cases of single coronary artery had been reported (Smith[16]). Smith divides these cases into three groups according to the distribution of the single vessel. Our case belongs to his Group III, that is, a case in which it is impossible to differentiate two coronary branches, right and left. A single coronary artery is often a postmortem finding, without there having been any previous clinical symptomatology. In our case, symptoms and signs depended upon the abnormal connection of the single coronary artery with the right ventricle and also upon the presence of added malformations.

Blakeway[17] and Edwards[18] described a rare type of abnormality of the coronary artery associated with atresia of the pulmonary valve, intact interventricular septum, and normal homologous atrioventricular valve. The abnormal coronary vessel in such instances originates from several small blood channels in the right ventricle. In this respect, we share the view of Williams and associates,[19] who believe that, from an early embryonic stage, the presence of a valvular barrier at the pulmonary area forces the blood from the right ventricular cavity through the intertrabecular sinusoids, causing them to persist in an abnormal fashion; later, these channels coalesce and form a large vessel which communicates with the coronary system. In our case a similar mechanism may be postulated, although atresia of the pulmonary valve was not present; however, stenosis of this structure was severe. This could very well have forced the blood to flow through the abnormal vessel in a right-to-left direction; this situation might also have been responsible for the presence of multiple smaller vessels which originated from the common vessel leading from the right ventricle into the coronary artery through the thickness of the right ventricular wall.

In so far as we are able to ascertain, this case is the only one of its kind in which a complex malformation of the coronary arteries is associated with a trilogy of Fallot.

Marked cyanosis and important desaturation of peripheral arterial blood could easily be accounted for by the right-to-left shunt present at the atrial level. However, right ventricular pressure was higher than systemic pressure, and filling of the abnormal coronary vessel from the right ventricle, as demonstrated by the angiocardiogram, makes it quite likely that part of the right-to-left shunt could be effected through this path, although blood gas analysis did not substantiate this assumption.

Because right ventricular systolic pressure was higher than aortic systolic pressure, we may assume that a good portion of the right ventricle, and probably of the left ventricle, received venous blood during systolic ejection of the right ventricle through the abnormal coronary vessel. However, it must be mentioned that no clinical or electrocardiographic signs indicated myocardial ischemia. This fact is not wholly surprising since the right ventricle seems to withstand anoxia much better than does the left ventricle.

Furthermore, it is a well-known fact that patients in whom the right coronary

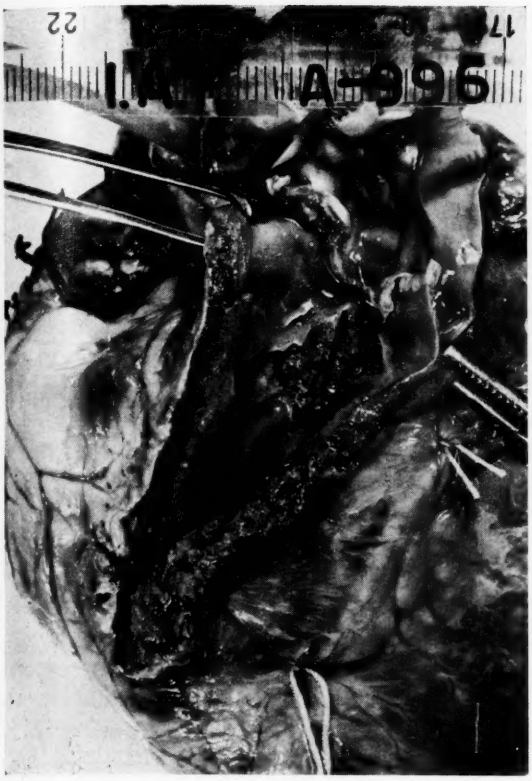

Fig. *3A*. The infundibulum and the pulmonary artery have been opened to show the pulmonary valve and the crista supraventricularis. Notice the valvotomy and the partial resection of the crista.

artery emerges from the pulmonary artery have better tolerance and outlook than patients in whom the left coronary artery arises from the pulmonary artery; in the latter case there are clinical and electrocardiographic evidences of coronary insufficiency. The former patients usually have a normal myocardium,[20] whereas the latter usually show myocardial changes of the type commonly described in myocardial infarction after coronary occlusion of sclerotic origin. Authors who are well versed on the subject[2,18] agree that the most important factor for ischemia is the low perfusion pressure of the coronary arteries, and not the low content of oxygen in the blood, as proved by the absence of such ischemic manifestations in severely cyanotic patients with congenital heart malformations in whom, despite a very low content of oxygen in the blood which supplies the myocardium, there are no ischemic manifestations. In our case the markedly elevated right ventricular pressure was able to maintain a good perfusion pressure of the coronary arterial system.

The diagnosis of the anomalous connection of the coronary artery with the right ventricle is difficult to establish. Up to the present time, only 7 patients have been suspected preoperatively of having this malformation.[7,9,13] A great number of the other cases reported have been diagnosed variously as patent ductus arteriosus,[5,10,13,21,22] or as ruptured aneurysm of a sinus of Valsalva into one of the right cardiac chambers.[23,24] These diagnoses have been due, in all likelihood, to the frequent presence of a continuous murmur (machinery type) or a systolic-diastolic murmur at different areas of the precordium. In the case of an anomalous coronary artery of the type under discussion there are some features which might lead to the correct diagnosis. Such are the atypical location of the murmur, usually at a very low portion of the precordium; the superficiality of the auscultatory phenomenon, which we find quite suggestive; and, finally, the

Fig. *3B*. Notice the catheter introduced into the ostium of the single coronary artery which arises from the right anterior sinus of Valsalva.

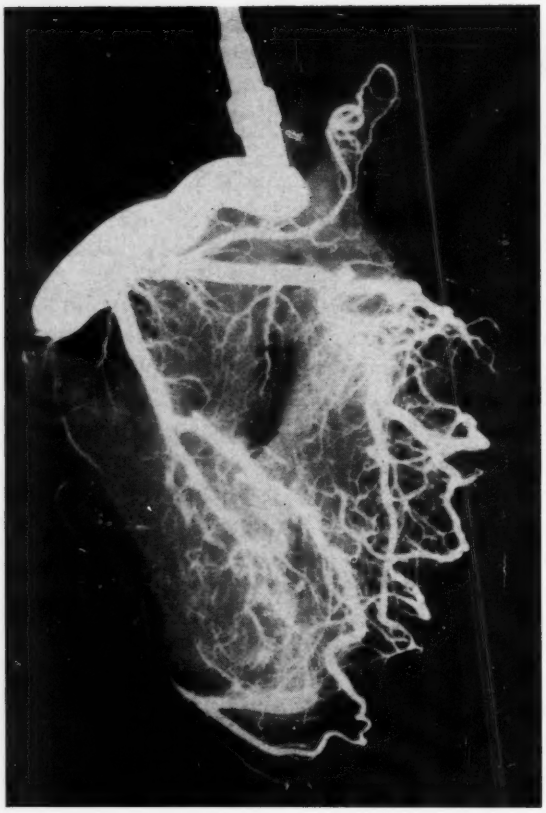

Fig. *4A*. Postmortem injection of the coronary network. Injection of the opaque substance at a greater pressure at the proximal end of the coronary artery, at the level of the single ostium. Notice the two important branches arising from the main vessel which supply the entire left ventricle and part of the right ventricle giving off numerous collateral vessels which anastomose profusely.

diastolic component of the continuous or systolic-diastolic murmur, which is considerably louder than the systolic component.

Our patient had a double murmur which was heard over practically all of the precordial area. The systolic component was louder at the pulmonary area, probably because of the presence of pulmonary valvular stenosis. This finding, in combination with cyanosis, the radiologic findings on the heart, and the electrocardiographic pattern, led us to suspect tetralogy of Fallot. However, the diastolic murmur, with its maximal intensity within the apex, and the superficial character which we have mentioned, made us suspect that there was an abnormal coronary arteriovenous shunt. The diagnosis of such a shunt was especially likely in the absence of clinical or other features indicative of pulmonary atrioventricular fistula, rupture of an aneurysm of the sinus of Valsalva into the right cardiac chambers, etc. Hemodynamic and angiocardiographic studies confirmed this suspicion. The conventional x-ray film and electrocardiogram proved of little aid in the diagnosis of this type of coronary abnormality.

The majority of authors agree that once this coronary abnormality is correctly diagnosed, the patient should be operated upon. Generally speaking, the risk of operation should not be extreme. Indeed, in both of the patients who died postoperatively, death could not be attributed to ligation of the abnormal vessel. However, in one patient,[9] myocardial infarction supervened as a result of ligation of the coronary artery; but it was successfully treated with the usual medical measures.

On the contrary, there is no agreement as to which is the best site for placement

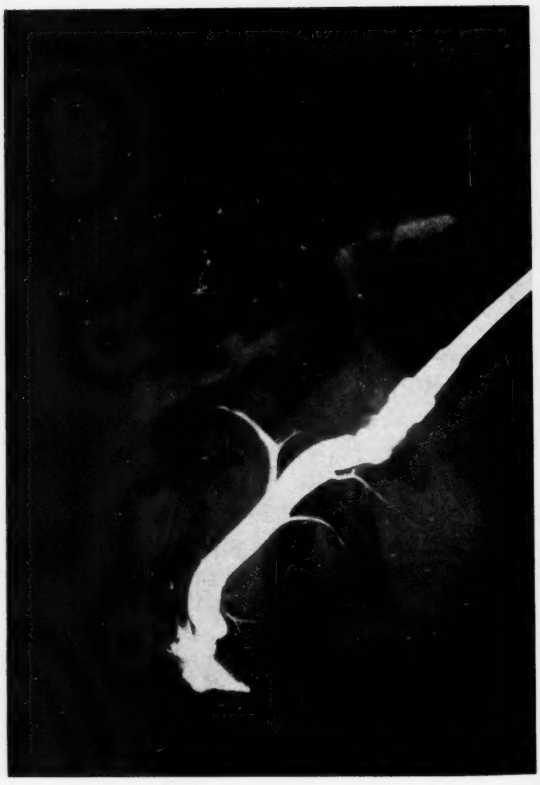

Fig. *4B*. The injection of the opaque substance was made with low pressure at the distal end of the surgical ligature of the coronary vessel. Notice the branches arising at obtuse angles in the distal sense. The right ventricle begins to fill with the opaque substance.

of the ligature on the coronary vessel. Some[13] postulate that the malformation should be occluded at the site of its abnormal connection and afterward ligated proximally to the origin of the aneurysm. Others[8,15] have merely ligated the vessel once they are satisfied that no electrocardiographic disorders of any consequence appear with transient occlusion. We believe that each patient should be considered individually and treated accordingly. This depends upon the anatomy of the patient as visualized by the surgeon at the time of operation. The minor anatomic details that cannot be visualized preoperatively will then become apparent. The surgical technique will vary accordingly. A careful analysis of the associated abnormalities should be made and the risk involved in their treatment carefully evaluated.

Summary

We have described a case of multiple and complex malformations of the coronary arterial system, i.e., single coronary artery which gave off several branches, one of which connected abnormally with the right ventricular cavity so as to produce a shunt. In addition, there was severe pulmonary stenosis with a high right ventricular pressure. This, in turn, maintained a right-to-left shunt through the abnormal coronary vessel. Another, similar shunt was present at the atrial level through an atrial septal defect.

These malformations were suspected clinically. Specialized studies (catheterization and angiocardiography) confirmed the diagnosis. The patient was operated upon for ligation of the abnormal coronary vessel and correction of the pulmonary stenosis. He died as a result of cardiac arrest.

The hemodynamic pattern of this unusual case is discussed.

We are greatly indebted to Dr. Madison S. Spach, from the Department of Pediatrics, Duke University Medical Center, Durham, N. C., U.S.A.; and to Dr. Jorge Espino Vela, Chief of the Department of Congenital Heart Diseases, Instituto Nacional de Cardiología de México, México, D.F., for their help in the revision and translation of this paper.

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Clinical pathologic conference

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Paul Adams, Jr., M.D.
Paul Winchell, M.D.
Richard G. Lester, M.D.
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DR. LUCAS: This patient was first seen at the University of Minnesota Hospitals, in 1959, at the age of 19 years. The case history reveals that he was born of a diabetic mother after a 7-month gestation. At the time of birth the patient had been considered to be normal, but development and the pattern of gain in weight were poor. A cardiac murmur was detected when he was 6 months old. The patient showed improvement in growth and development at about 1 year of age, and, with the exception of occasional upper respiratory infections, he was thereafter symptom-free until the age of 9 years. At that time, dyspnea developed, becoming fairly severe during the next several months. Cardiomegaly was noted on roentgenographic examination Upon the diagnosis of congestive cardiac failure, a digitalis preparation was administered.

Right-sided cardiac catheterization had been performed elsewhere when the patient was 10 years of age. The results of this procedure (Table I) were interpreted as indicating a large left-to-right shunt of about 6 liters per minute at the ventricular level. Pulmonary arterial pressures approached systemic pressures. The oxygen saturation of the femoral arterial blood was at the 92 per cent level, suggesting an additional right-to-left shunt. Simultaneous determination of pulmonary arterial blood oxygen saturation revealed a level of 87 per cent.

By the age of 12 years, the patient had improved significantly, and the administration of digitalis was discontinued. He was essentially symptom-free until the reappearance of dyspnea and easy fatigability at 17 years of age. During the next 2 years, until the patient was admitted to the University of Minnesota Hospitals at the age of 19, his condition remained essentially unchanged.

At this time the patient was a large, well-developed young man, without cyanosis or clubbing. Examination of the heart revealed normal rate and rhythm, with no palpable thrill. A Grade 3 (on the basis of 1-6) harsh systolic murmur was heard along the left sternal border, maximally discernible at the third and fourth left intercostal spaces. The murmur was transmitted toward the apex. A soft diastolic murmur was heard at the second intercostal space and along the left sternal border. The second sound in the pulmonic area was markedly accentuated. On the basis of further studies to be presented, the patient was subjected to operation with the aid of extracorporeal circulation. The

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Table I. *Summary of data of both cardiac catheterizations*

Age of patient (yr.)	*Pressure (mm. Hg)*				*Blood oxygen saturation (per cent)*						*Total pulmonary resistance (dynes sec. cm.$^{-5}$)*
	RA	*RV*	*PT*	*FA*	*IVC*	*SVC*	*RA*	*RV*	*PT*	*FA*	
10*	7/1	90/0	94/49 64†	92/49 63†	67	57	63	86	87	92	570
19	3†	95/3	108/54 65†	130/75 93†	—	60	66	91	90	96	200

*Catheterization performed elsewhere.
†Integrated mean pressure.
RA: Right atrium. RV: Right ventricle. PT: Pulmonary trunk. FA: Femoral artery. IVC: Inferior vena cava. SVC: Superior vena cava.

patient died during the immediate postoperative period.

Dr. Adams, would you please discuss the diagnostic possibilities suggested by the material covering the patient's first 17 years.

DR. ADAMS: The actual course of the disease in this patient represents one of several possible patterns in patients with ventricular septal defect. In infants with severe manifestations, including improper pattern of growth, one may observe spontaneous improvement at about 1 year of age. As symptoms in the infantile period may result from a large left-to-right shunt, so improvement may follow if the shunt becomes reduced, possibly as a result of an increase in pulmonary vascular resistance. With the exception of an episode of congestive heart failure at age 9, this patient did reasonably well until he was about 17 years old. The dyspnea and fatigue appearing at that time may have resulted from organic pulmonary vascular changes that may complicate chronic pulmonary hypertension. An increase in pulmonary vascular resistance would reduce the size of the left-to-right shunt, but, at the same time, a right-to-left shunt might increase in magnitude or might appear. An alternative explanation for the cardiac failure observed at 9 years of age is that an attack of pneumonia may have caused myocardial weakness through toxemia. Pneumonia is a frequent complication of congenital cardiac disease associated with large left-to-right shunts.

Two phenomena are still puzzling to me. One is the closeness of the levels of oxygen saturation in the pulmonary and in the femoral arteries. This might suggest a common mixing chamber as seen, at times, in cases of single ventricle. The other point is that cyanosis has not been mentioned in the clinical history. Since the systemic arterial blood was desaturated when the patient was 10 years old, I would suspect that cyanosis might have accompanied his symptoms if they arose from increasing pulmonary resistance. Was the patient ever cyanotic?

DR. LUCAS: He was never noted to be cyanotic. Dr. Winchell, you treated this patient on his admission to the University of Minnesota Hospitals. Would you comment on your findings.

DR. WINCHELL: The physical findings at age 19 have been reviewed, and I need not repeat them. The electrocardiogram (Fig. 1) revealed normal sinus rhythm. The P-R interval was prolonged, measuring 0.21 second. The mean manifest electrical axis of the QRS complex was +60 degrees. Precordial leads showed evidence both of right ventricular systolic overload and of left ventricular diastolic volume overload. Dr. Lester, would you comment on the radiologic findings.

DR. LESTER: Radiologic examination of the thorax (Fig. 2) reveals marked cardiomegaly. The main pulmonary arterial segment is very prominent, and there is diffuse enlargement of the intrapulmonary arterial vessels. The left atrium does not

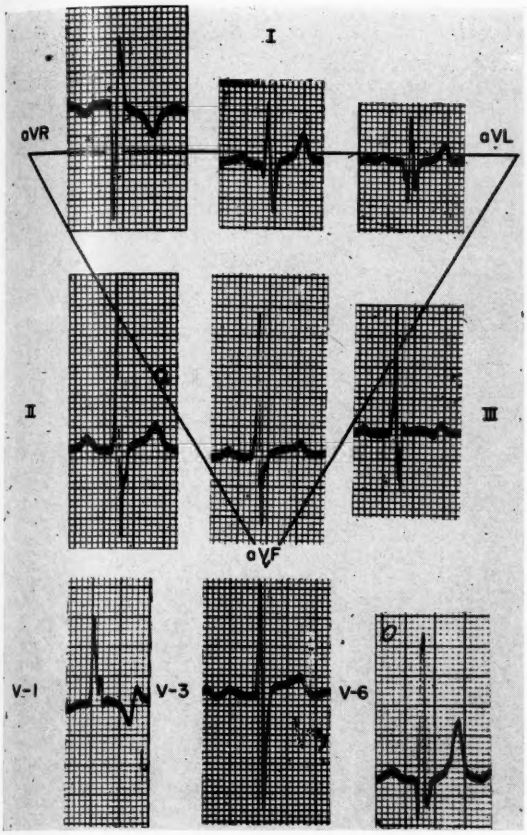

Fig. *1*. The electrocardiogram. See text.

appear to be enlarged. The picture suggests a large left-to-right shunt with associated pulmonary hypertension.

DR. WINCHELL: The working clinical diagnosis was ventricular septal defect with pulmonary hypertension. A second cardiac catheterization was decided upon, in order to establish more precisely the hemodynamic state.

The results of the second catheterization suggested a massive left-to-right shunt at the ventricular level. The pulmonary arterial pressure was unchanged from that observed on the first catheterization. The oxygen saturation of the femoral arterial blood was 96 per cent, and that of the pulmonary arterial blood was 90 per cent. Inhalation studies with methyl I^{131} were made, with sampling of blood from the right ventricle, right atrium, and superior vena cava. These indicated a left-to-right shunt at the ventricular level and no shunt at the levels either of the right atrium or of the superior vena cava. Studies using Renografin I^{131} and Cardiogreen were made by injecting each separately into the superior vena cava, right atrium, and right ventricle and recording in a femoral artery. No right-to-left shunt was detected. The calculated pulmonary resistance was observed to be in the normal range (200 dynes sec. $cm.^{-5}$). The next day a selective aortogram was made. Dr. Lester, would you discuss these findings.

DR. LESTER: The aortogram was made by injecting radiopaque material into the root of the aorta (Fig. 3). No extracardiac shunt could be demonstrated. On the basis of the aortogram, we excluded corrected transposition, aorticopulmonary communication, and coarctation of the aorta.

DR. WINCHELL: The foregoing findings led us to believe that this patient had a large ventricular septal defect with a large left-to-right shunt. Aortography appeared to have ruled out other complicating lesions, and the patient was considered to be a proper candidate for surgical correction of the ventricular septal defect. Dr. Lillehei, would you describe the operative procedure.

DR. LILLEHEI: After establishing extracorporeal circulation, we opened the right ventricle. This revealed a direct communication of the aorta with the right ventricle and a large ventricular septal defect. It was apparent that closing this defect by

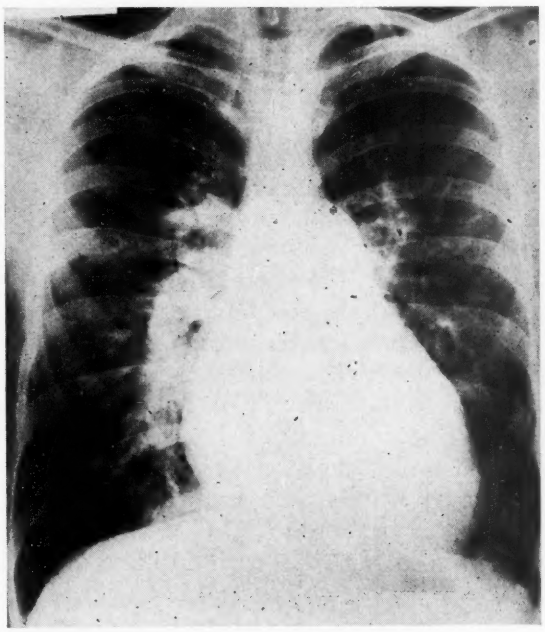

Fig. *2*. Posteroanterior roentgenogram of thorax.

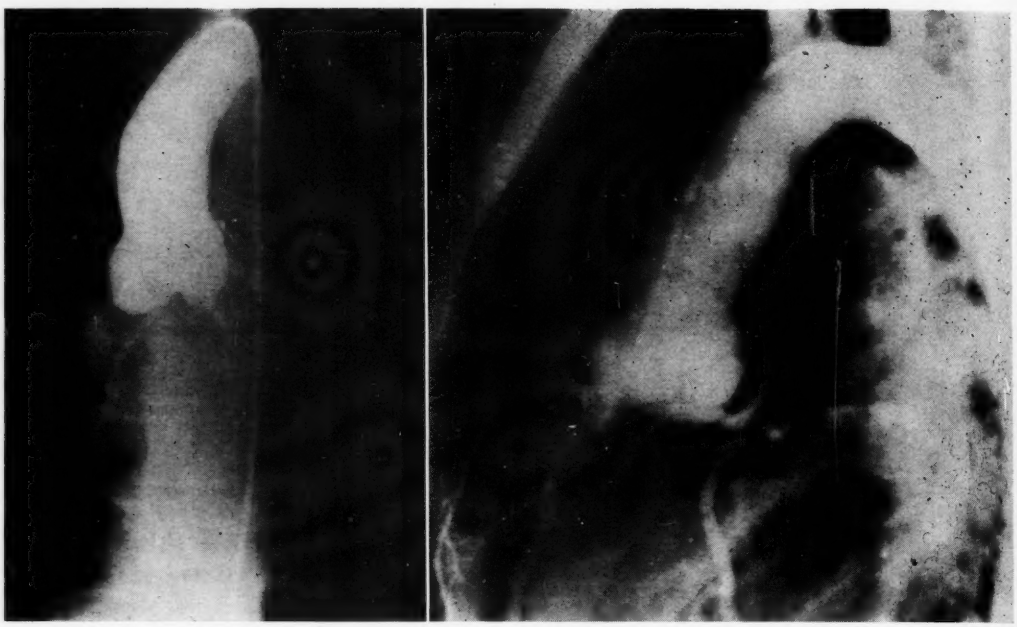

Fig. 3. Selective aortogram. *Left*: Anteroposterior view. Radiopaque material fills the ascending aorta and the coronary arteries. The root of the aorta overlies the spine and is farther to the right than is anticipated in normal subjects. The aortic valve appears to lie at a higher body plane than normal. *Right:* Lateral view. From the opacified ascending aorta it is apparent that the aortic origin lies more anteriorly than is normal. See text for further discussion.

directly opposing the edges would occlude the left ventricular outflow tract. Therefore, the corrective procedure involved placing a Teflon prosthesis in such a way as to divert the blood from the left ventricle into the aorta, while excluding the two ventricles from intercommunication.

DR. LUCAS: Dr. Edwards, would you please describe the pathologic findings.

DR. EDWARDS: Necropsy revealed that the heart was grossly enlarged and globular in shape. From the exterior the two great vessels appeared to be properly interrelated. At the level of the base of the right ventricle, however, the aorta, instead of curving downward to the left to take origin from the left ventricle, communicated with the right ventricle at about the same body plane as did the normally placed pulmonary valve. The aortic valve lay to the right of, and only slightly posterior to, the pulmonary valve. The communication of the aorta with the right ventricle lay postero-inferior to the parietal band of the crista supraventricularis and in front of the tricuspid valve at about the junction of the septal and anterior leaflets (Figs. 4 and 5).

A large ventricular septal defect was present, which likewise lay postero-inferior to the parietal band of the crista supraventricularis and extended down along the septal branch of the crista. When viewed from the left ventricular aspect, this defect was seen to lie in front of the junction of the anterior and septal leaflets of the mitral and tricuspid valves, respectively. Elsewhere, its edges were composed of muscle. The defect, which measured about 3 cm. in diameter, represented the only outlet for the left ventricle. No anatomic continuity existed between the left ventricle and the aorta. It was possible to make an incision which gave the initial impression that the left ventricle and the aorta were in continuity. Close inspection revealed, however, that the aortic and mitral valves failed to show the continuity which is normally present between these two structures. They were, in fact, separated by a mass of muscle which represented the superior rim of the ventricular septal defect (Fig. 5). Continuing with inspection of the specimen from this aspect, it was apparent that (1) the left ventricle emptied through the ventricular septal defect into

the outflow part of the right ventricle, and (2) that this part of the right ventricle, in turn, communicated with the aorta.

Surgical correction of the abnormal communication had been accomplished by the placement of a Teflon prosthesis in such a way as to create a tunnel from the left ventricle through the ventricular septal defect into the right ventricle and then to the aorta. The lower half of the Teflon septum had been sutured to the edges of the ventricular septal defect, whereas the upper half of the prosthesis was sutured to the right ventricular wall along a line about 1.5 cm. below the level of the attachment of the aorta to the right ventricle. Placement of this prosthesis, therefore, created a tunnel through the ventricular septal defect into that portion of the outflow part of the right ventricle from which the aorta arose. The subaortic part of the right ventricle was separated from the remaining portion of the right ventricle by the prosthesis (Fig. 5). In this way, blood entering the right ventricle was entirely diverted to the pulmonary trunk, whereas blood entering the left ventricle was carried through the afore-mentioned channel into the aorta, since the functional interventricular communication had been obliterated.

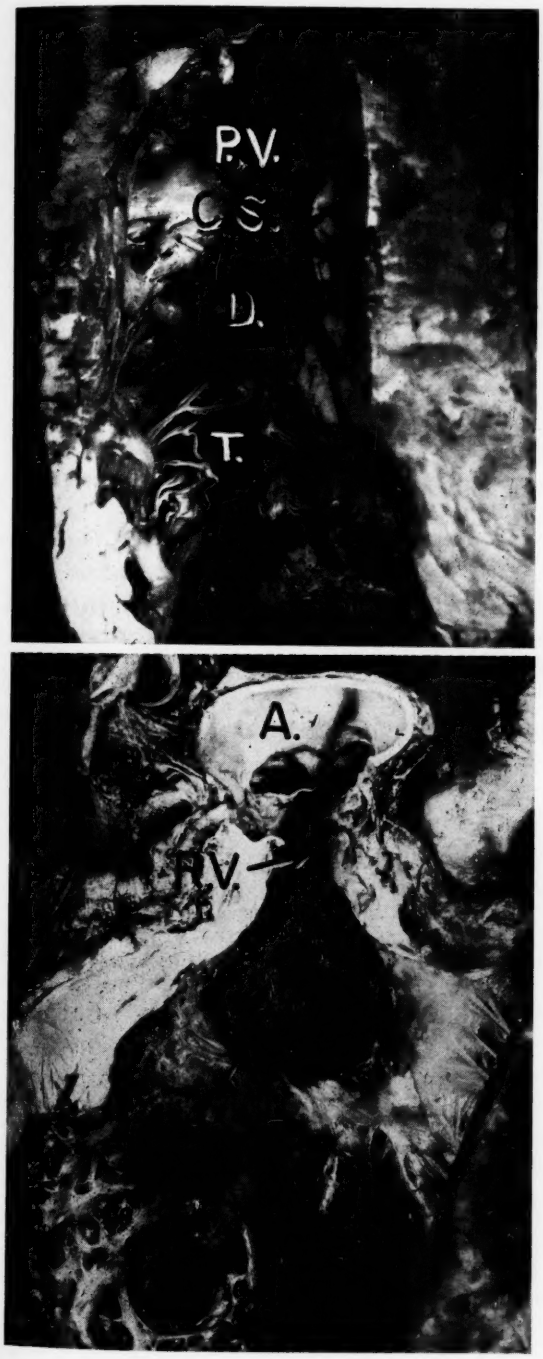

Fig. 4. *(For legend see opposite column.)*

The venous connections with the heart were normal. The mitral valve appeared to be competent, and the tricuspid and the pulmonary valves were essentially normal.

The right ventricular wall was thick, measuring up to 1.7 cm. in thickness, whereas the left ventricular wall measured about 1.5 cm. in thickness. The pulmonary trunk was wide, having a diameter of about 3 cm. The aortic diameter was about 2 cm. Three aortic leaflets were present: a right posterior, a left anterior, and a right ante-

Fig. 4. Specimen of heart. *Upper:* Right ventricular view. The interventricular communication (*D.*) has been obliterated by the placement of the Teflon felt patch described in the text. Above the ventricular septal defect lies the crista supraventricularis. In a more superior and anterior location lies the pulmonary valve (*P.V.*). The tricuspid valve (*T.*) lies postero-inferior to the defect. Communication between the aorta and the main part of the right ventricle has been obliterated by the prosthesis (*D.*). There is no obstruction in the tract leading to the pulmonary valve. *Lower:* Left ventricular view and ascending aorta. The prosthesis (*D.*) not only obliterates the interventricular communication but also allows communication of the left ventricle with the upper portion of the right ventricle (*R.V.*), from which the aorta takes exclusive origin. The apparent continuity between the left ventricle and the aorta is an illusion derived from the plane of dissection. In the intact state the only outlet for the left ventricle was the ventricular septal defect, whereas the aorta communicated directly with the right ventricle.

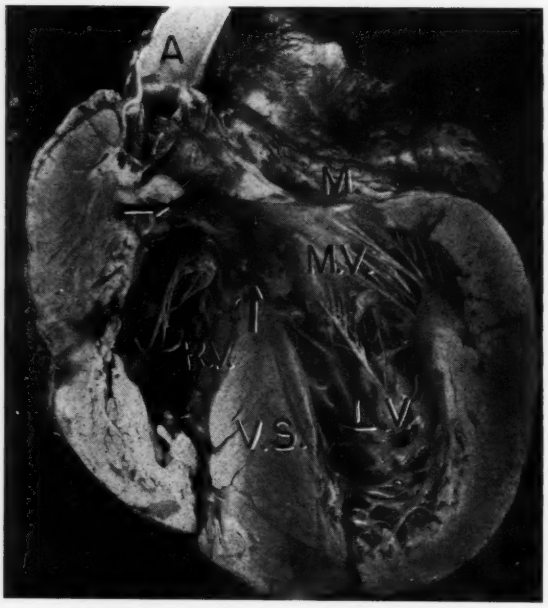

Fig. 5. Sagittal section through the ventricles of the heart, the aorta, and the region of the ventricular septal defect. The front of this specimen has been removed, and the view here shown is of the posterior portion of the specimen viewed from the front. The plane of dissection was such that the pulmonary valve is not shown, since it lay in the anterior portion of the specimen along with the anterior wall of the aorta. Between the arrows lies the prosthesis used to obliterate the interventricular communication. At the same time, this device allows communication of the left ventricle (*L.V.*) with that portion of the outflow tract of the right ventricle (*R.V.*) from which, in turn, the ascending aorta (*A.*) takes origin. In contrast to the normal situation, the anterior leaflet of the mitral valve (*M.V.*) here is separated from the aortic valve by a mass of muscle (*M.*), which represents the upper wall of the ventricular septal defect. *V.S.*: Muscular portion of ventricular septum.

rior. Arising above the right posterior aortic sinus, the right coronary artery proceeded in the right atrioventricular sulcus without giving off any major branches to the anterior aspect of the heart. The left coronary artery arose above the left anterior sinus and branched in an essentially normal manner, giving off both anterior descending and circumflex branches.

Histologic examination of the lungs revealed extensive alterations in the arterial bed (Fig. 6). Large muscular arteries showed pronounced medial hypertrophy. Some vessels of this category, as well as some small muscular arteries, showed intimal lesions. Some were characterized by nonspecific fibrous thickening, with or without focal hyalinization of the vessel wall, whereas other intimal lesions showed formations of the characteristic "plexiform lesion."

Beyond zones of luminal narrowing by intimal lesions, the media of the arterial wall was thin and the lumen widened, at times excessively. The arterioles and many small muscular arteries were thin walled and associated with wide lumina. The picture of the vascular bed was that previously termed a "high resistance–low reserve" type[2] or "hypertensive pulmonary vascular disease, Grade IV."

Dr. Neufeld, you were involved in a clinical pathologic study of a group of cases in which both great vessels arose from the right ventricle, as in this case. Would you care to make some remarks about this subject.

DR. NEUFELD: When both great vessels arise from the right ventricle, pulmonary stenosis may or may not be associated. I shall confine my remarks to cases which present without pulmonary stenosis, since they are more pertinent to the case here discussed.

We studied 8 cases of this malformation occurring without associated pulmonary stenosis.[3] In each the clinical picture resembled that seen among some cases of large ventricular septal defect with pulmonary hypertension. Clinically, cyanosis and clubbing were very common. A systolic thrill was usually present and was associated with a systolic murmur of the type present in ventricular septal defect. The second pulmonic sound was accentuated in each case. Electrocardiographic findings were of considerable interest. In 7 of the 8 cases the mean manifest electrical axis of the QRS complex lay between −30 and −170 degrees, and the instantaneous QRS vector in the frontal plane showed a counterclockwise loop with its main mass above the zero line. Roentgenographic examination revealed features usually present in ventricular septal defect with pulmonary hypertension.

From a hemodynamic point of view, one could divide the 8 cases previously studied into two groups, one with high pulmonary vascular resistance and the other with low pulmonary vascular resistance. In most of the cases the ventricu-

lar septal defect was large, and, therefore, the pressures on the left and right sides were equal. Since volume of pulmonary flow depends on the relative levels of pulmonary and systemic resistance, with lower pulmonary resistance the pulmonary flow would be greater than the systemic flow. When pulmonary flow is extremely high, and when good mixing occurs in the right ventricle, the level of oxygen saturation of pulmonary arterial blood may be nearly equal to the level of oxygen saturation of the highly oxygenated blood in the systemic arterial system.

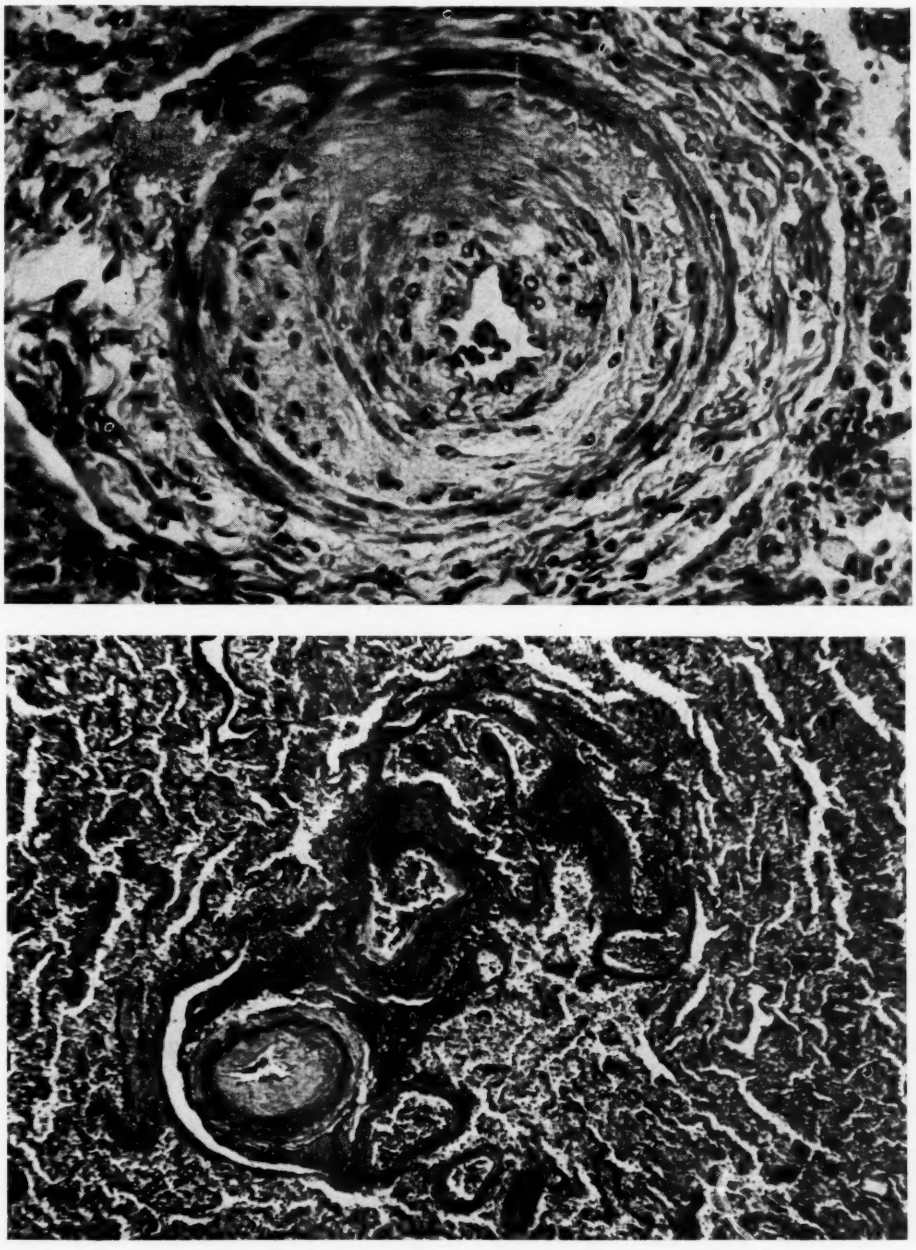

Fig. 6. Photomicrographs of pulmonary arterial vessels. *Upper:* A muscular pulmonary artery shows almost complete obliteration of the lumen by pronounced nonspecific concentric fibroblastic proliferation of the intima (hematoxylin and eosin, × 200). *Lower:* A pulmonary artery shows intimal thickening with fibrous tissue. Beyond, a branch shows tortuosity and considerable dilatation, with thinning of the wall. The pattern is commonly found in pulmonary hypertension together with pronounced increase in pulmonary vascular resistance (elastic tissue stain, × 100).

In the group of cases with high pulmonary flow the differential diagnosis, as mentioned by Dr. Adams, includes single ventricle and origin of both great vessels from the right ventricle. Determination of the anatomic positions of the semilunar valves and of the great vessels may help to differentiate these two conditions. When both great vessels originate from the right ventricle, the two great vessels are parallel in anteroposterior as well as in lateral views, and the aortic and pulmonary valves are located at about the same body level.

In the case presented here the electrocardiogram showed a mean axis of the QRS complex of +60 degrees in the presence of evidence for right ventricular systolic overload in the precordial leads. The vectorial loop in the frontal plane was directed counterclockwise, but a substantial portion of it lay below the zero line. Thus, the electrocardiogram suggests the usual type of ventricular septal defect.

To the best of my knowledge, no aortogram from a patient with this condition later proved at necropsy has yet been presented in the literature. Dr. Lester, would you now, in retrospect, discuss the features of the aortogram.

DR. LESTER: Review of the aortogram shows no evidence of an extracardiac shunt. The ascending aorta lies to the right of the midline, excluding the diagnosis of corrected transposition of the great vessels.

Careful analysis of the films shows that the aortic sinuses (Valsalva) are slightly higher than is normal; the aortic valve is at the projected level of the pulmonary valve. In addition, the ascending aorta is slightly anterior to its normal position, particularly at the level of its origin. The ascending aorta points in a vertical direction, instead of pointing backward and to the left toward the left ventricle. Furthermore, in the frontal view, the aortic sinuses are superimposed on the spine, without the normal turn toward the left ventricle.

Analysis of the position of the coronary arteries shows that the most proximal portion of the anterior descending branch of the left coronary artery takes a more horizontal course toward the left than is seen in the normal. This appears to be due to the abnormally right-sided position of the aortic origin as seen in the frontal view. The most proximal portion of the circumflex branch of the left coronary artery is also displaced somewhat toward the right, so that the proximal portion of this branch is superimposed on the left border of the dorsal spine.

In retrospect, the position of the aortic sinuses is abnormal. This should strongly suggest the anomaly that was proved to be present.

We have found that the diagnosis of origin of both great vessels from the right ventricle is best established by selective angiocardiography; the injection is made into the right ventricle. It may also be confirmed by left ventriculography in cases in which the aortographic findings arouse suspicion of this anomaly. In the latter situation the catheter may be passed through the aortic valve into the left ventricle and an injection made in this area.

DR. WINCHELL: Dr. Lillehei, since it seems possible to distinguish this malformation from the usual ventricular septal defect and from single ventricle, would you discuss the importance of the differential diagnosis from the surgical point of view, as well as the various surgical approaches and techniques used in treating this malformation.

DR. LILLEHEI: The success of the surgical treatment of almost any condition has a direct correlation with the accuracy of preoperative diagnosis. Since diagnosis is never perfect, an experienced and discerning surgeon often must and frequently can make successful allowance for varying pathologic lesions encountered unexpectedly at the time of operation.

For this reason we have insisted for several years that every one of our patients who has a ventricular septal defect associated with severe pulmonary hypertension undergo preoperative selective aortography, and often, at the same time, left ventriculography.[4] This practice has been extremely rewarding in enabling us to identify preoperatively some of the serious conditions which may be associated with ventricular defect. The forewarned surgeon is thereby forearmed, and the risk for the patient is substantially lessened.

In the case under discussion here, as has been indicated, the great vessels appeared from the exterior aspect to have a

normal interrelationship, as is characteristic in this condition. Upon opening the right ventricle of this patient, however, we noted some important anatomic differences from the usual types of ventricular defects. Dr. Edwards has already commented on several of these differences. From the surgical standpoint, perhaps the most important of these was that, although the defect in this patient was large, the ventricles were also very large. With the heart arrested (by selective hypothermia[5]), we could easily have approximated the edges of the defect, but to do so would clearly have occluded the outflow of blood from the left ventricle. Closure was therefore undertaken by placing a Teflon prosthesis in such a way as to obliterate the interventricular communication and to direct the blood from the left ventricle unimpeded into the aorta.

The pressures measured directly at the time of operation in this patient were of interest. These measurements confirmed the pulmonary hypertension noted when the cardiac catheterizations had been performed. The presence of residual pulmonary hypertension after the repair was considered to be indicative of high levels of pulmonary vascular resistance.[6]

After the reparative procedure the heart took over well from the extracorporeal circulation. The patient was awake immediately after operation, and his appearance, blood pressure, and cardiovascular status were excellent in the early postoperative period. About 24 hours postoperatively, faint icterus was noted, but, since all vital signs were good, not much significance was attributed to this observation. During the next 6 to 8 hours, however, the jaundice deepened rapidly and the brachial blood pressure declined for the first time. The venous pressure and blood volume remained normal. Septicemia was suspected, but all blood cultures ultimately proved to be sterile.

The postmortem examination disclosed acute massive necrosis of the liver, but no discernible cause of this unusual complication was obvious. The most probable hypothesis appears to be that during the bypass procedure the somewhat soft plastic catheter in the inferior vena cava became kinked for a prolonged period while the attention of those at the operating table was directed toward repairing the cardiac defect.

DR. EDWARDS: Dr. Lucas, evidence relating to the pulmonary vascular bed is somewhat paradoxical. On the one hand, the data of the cardiac catheterizations indicate high values of pulmonary blood flow and normal, or near normal, pulmonary vascular resistance. On the other hand, the operative pressure studies and the histology of the pulmonary vascular bed point in an opposite direction. The persistence of significant pulmonary hypertension after closure of the interventricular communication and the type of pulmonary vascular disease suggest that the pulmonary vascular resistance was of high order.[7,8]

DR. LUCAS: In this case, the values calculated for pulmonary blood flow and resistance were probably influenced by the physiologic artifacts that this condition imposes. The calculated values for pulmonary resistance depend, of course, on pulmonary flow rates as well as pulmonary arterial mean pressure. In the cardiac abnormality present in this patient, origin of both great vessels from the right ventricle, it is questionable whether assessment of pulmonary flow can be made from the oxygen values of blood in the pulmonary trunk. It is apparent from the anatomic arrangement that an obligatory "shunt" of all blood from the left ventricle to the right ventricle occurs. Some of the arterialized blood in the right ventricle, although arriving through the ventricular septal defect, is not "shunted" blood in the usual sense; this is because some of this blood is going to a normal goal, the aorta, albeit through an abnormal anatomic route. In fact, a common chamber exists, the right ventricle, which supplies both great vessels with mixed arteriovenous blood. Therefore, increased oxygen saturation in the pulmonary trunk does not necessarily reflect a high pulmonary flow, but may be an expression of mixing in the common chamber, the right ventricle. Therefore, the data of the cardiac catheterizations do not accurately reflect the true functional state in this patient.

Diagnosis: Origin of both great vessels from the right ventricle, without pulmonary stenosis

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Annotations

Tracers and lymph

Additions to our knowledge of the anatomy and functions of the lymphatics have been slow in the 2,000 years since these vessels were first seen by members of the Alexandrian School about 300 B.C., and in the 340 years since the lacteals were described by Aselli in 1622.[1] An annotation in *Lancet*, April, 1959, relates some of the studies of the lymphatic system from the time that William Hunter stated in 1784 that, "The lymphatics are the absorbing vessels all over the body," to the present-day studies with isotopic tracers.[2] Even the use of "tracers" is not new, as exemplified by the work of Mendel,[3] published in March, 1896, two months prior to Starling's classic in the same volume.[4]

In his paper, Mendel reported that the time from intravenous injection of sodium iodide to its appearance in the lymph of the thoracic duct of dogs was 4 minutes. Since then, other investigators using various tracer substances have studied the rates of uptake by, and of flow in, the lymphatic vessels. Haynes[5] cited that bromphenol blue traveled from vein to thoracic duct in 2.5 to 6.5 minutes, and to skin lymphatics in 0.5 minute, and that the rate of movement of vital red from vein to thoracic duct was from 2 to 8 minutes. Iodinated albumin and dextran have been timed from blood to thoracic duct in 7 to 10 minutes,[6] and horse serum injected subcutaneously in dogs has been detected in the lymph of the thoracic duct in 40 minutes and in blood in 3.5 hours.[7] Albumin injected into the hind paw of dogs has been reported to be in cervical lymph in 10 seconds, and patent blue V injected into the hind paw of rabbits to appear in groin lymph in 20 to 30 seconds (2 to 3 seconds after absorption).[8] In man, Evans blue has been described, on one occasion, to require 20 to 30 minutes to appear in the thoracic duct after intravenous injection.[9] Patent blue V, 0.1 c.c. of 11 per cent aqueous solution, injected intradermally in man formed streamers 15 cm. long in 5 minutes, but when 0.05 c.c. of 1 per cent solution was used, it was 20 minutes before streamers 10 to 15 cm. long were visible.[10]

The foregoing variations in the rates of movement from veins to the lymph of the thoracic duct or from skin to lymph may be reflections of differences in the quantity of substance injected and in the sizes of "tracer" substances, resulting in various rates of escape from veins and rates of uptake by lymphatic vessels. None of these experiments permitted accurate estimation of the rate of flow of fluid in a given segment of extremital lymphatics. The difference in paw–thoracic duct time and vein–thoracic duct time, however, indicates that more time is required for diffusion from the veins into the lymphatics than for flow from one point of the lymphatic system to another. The rapid flow rates reported suggest that the volume of the lymphatic system is small. For the flow time to be so short, the volume per minute collected from the thoracic duct (about 1 c.c. per minute in man or in dog) must represent a large fraction of the total volume in the system. Determination of precise rates of flow within the lymphatic channels would be important in the evaluation of the role of the lymphatics in the transport of fluid from normal or edematous extremities and in the determination of the size of this compartment itself. For measurement of flow, as distinguished from combined uptake and flow, it is necessary to collect lymph containing tracer or to monitor for tracer at two sites along a lymphatic channel cephalad to the site of injection and absorption of a substance taken up and transported only by the lymphatics. Most of the smaller molecules of dyes used to visualize lymphatics,[11] salts and radiopaque media[12] are absorbed by venous capillaries as well or escape rapidly from the lymphatics, and, therefore, are not adequate. Many substances of large molecular weight can serve, but well-tagged albumin is probably the most practical tracer to utilize at this time. The search for such a tracer originated in 1862, when Von Reklinghausen demonstrated lymphatic uptake of egg yolk, 1 micron in diameter. Since that time, increasingly larger particles have been studied. Among others, Auspitz, in 1871, used rice starch particles that were 8 micra in diameter, and Allan, in 1956, showed that paraffin-asphalt spheres up to 22.5 micra in diameter entered the lymphatics.[13] Studies such as these to determine the limit of the size of particles taken up by the lymphatics have inferred that there is unidirectional movement and that large particles, once having entered, do not escape from the lymphatics. This is a widespread assumption with regard to the return of proteins to the circulating system. Results of infusions into the leg lymphatics of a dog and recovery from the thoracic duct suggest that particles with a molecular weight greater than 3,200 do not leave the lymphatics once they have entered.[14] Barnes and Trueta[15] provide further evidence that the larger protein molecules are absorbed mainly or entirely by the lymphatics, in their report that rabbits injected in the legs with snake venom after all lymphatics had been severed survived, whereas intact animals died. This is supported clinically by

the observation that edematous fluid from subjects with obstructive types of edema is viscous and yellow because of the concentration of protein, whereas the edema fluid from subjects with congestive heart failure is relatively low in protein because this is returned by the lymphatics in essentially the same proportion as it is lost from the capillaries.

Only after precise measurement of the rates of uptake of substances by, and rates of flow within, the lymphatics will it be possible to evaluate the importance of the exact size and volume of the enclosed lymphatic system. The contents and size of this compartment must be considered in any turnover or space study based upon concentration and content of the serum compartment, especially when diffusable tracers are used.[16] It is conceivable, because of the diffusability and free exchange of smaller molecules, that, with the exception of transport of particles and large molecules, this system may be considered to be a channel of flow in the unenclosed extracellular fluid or interstitial fluid space. It is also possible, however, that knowledge of these rates may prove to be valuable in studying procedures or drugs which can influence rates of uptake and transport of even the smaller molecules by the lymphatics, thereby leading to better methods of therapy for all types of edema.

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On the cause of S-T-segment shift of electrocardiogram in myocardial infarction

In studying the causes of S-T-segment shifts in myocardial infarction, we used the phenomenon described by M. G. Udelnov in 1955. He showed that the application of necrotic tissue to the unaffected heart produces at the place of contact a relaxed zone of myocardium which does not take part in the systole of the heart. The appearance of this zone, called pre-necrotic, leads to a marked shift of the S-T segment of the electrocardiogram, similar to shifts which are observed in myocardial infarction.

For the elucidation of the cause of this phenomenon it was necessary to understand the mechanism of the action of the necrotic tissue on the heart. We supposed that it had an ionic nature.

In the first series of experiments, made on frogs and rabbits, the pieces of necrotic tissue were applied to the heart in situ; the pieces were enriched with potassium, sodium, or calcium, or, conversely, the pieces were applied after preliminary extraction of these ions. During the experiments we found that

the application of necrotic tissue can only influence the myocardium if the tissue contains potassium ions. The presence or absence of calcium and sodium ions does not influence the ability of necrotic tissue to cancel bioelectrical and contractile activity of myocardium which is in contact with it.

On the basis of these experiments, the preliminary conclusion reached was that the action of necrotic tissue on the neighboring myocardium is connected with the transfer of potassium ions from necrotized tissue to intact regions of myocardium in contact with it.

This conclusion was checked in the second series of experiments in which necrotic tissue was applied to hearts in situ of rabbits and frogs, and by means of the flame photometer a quantitative determination of the content of potassium and sodium was made in necrotic tissue before and after its application to the myocardium, in the myocardium in contact with the necrotic tissue, and in remote parts of the myocardium. The experiments showed that in the case of necrotic tissue applied on healthy myocardium, potassium ions are really transferred from necrotic tissue into the adjoining regions of the heart. This leads to the appearance of electrocardiographic S-T-segment shifts of the type observed in cases of myocardial infarction.

Therefore, it was necessary to make clear whether there is such a transfer of potassium ions from the necrotic zone into contiguous parts of the myocardium under the conditions of the appearance of a necrotic area in the heart itself.

We ligated the left anterior descending coronary artery in rabbits, and at different times after placement of the ligature (from 5 minutes to 3 months) we determined the content of potassium, sodium, and chloride in the zone of ischemia or necrosis and in the contiguous regions, and—for comparison—in healthy parts of the myocardium, i.e., in the posterior wall of the left ventricle. The data of the biochemical analysis were compared with electrocardiograms made before the rabbits were killed.

We found that, in the zone of necrosis, potassium content strongly decreases in comparison with the normal, but that the content of sodium and chloride is significantly increased.

In the regions of myocardium contiguous with the necrotic region the amount of potassium increases in comparison with normal. Content of sodium and chloride decreases somewhat in comparison with that in healthy tissue of the left ventricular posterior wall.

The increased amount of potassium in tissues contiguous with the area of necrosis is observed for approximately 25 days and coincides with significant S-T-segment shift, and with the changes of the T wave of the electrocardiogram.

The data obtained allow us to say that, in the mechanism of formation of a pre-necrotic zone in the heart, which produces the S-T-segment shifts of the electrocardiogram typical for myocardial infarction, the exchange of potassium ions plays the dominating role.

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Effective coronary perfusion pressure

The principal determinants of coronary blood flow are central aortic perfusion pressure and venous pressure in the right atrium.[1] Central aortic pressure drives blood into the coronary arteries, and right atrial pressure resists their emptying. Pressure in the right atrium not only resists flow from the coronary sinus, which drains most of the blood delivered by the left coronary artery, but also flow from the anterior cardiac veins, which drain most of the right ventricular coronary flow. Thebesian venous drainage into the right atrium represents a very small amount of the total coronary venous return, but this too is resisted by right atrial pressure.

Perhaps because the right atrial pressure is normally so low (3 or 4 mm. Hg mean), the significance of its resistance to coronary flow is sometimes forgotten. In studies on hemodynamic changes associated with experimental pericardial tamponade, Binion, Morgan, Welch and Sarnoff[2] recently demonstrated the practical importance of considering *both* of the two principal determinants of coronary flow. In experimental shock their dogs with cardiac tamponade died when mean aortic pressure fell to 50 mm. Hg, whereas control dogs without tamponade survived mean aortic pressures of 25 mm. Hg. The difference in survival was attributed to the elevated right atrial pressure in dogs with cardiac tamponade. The useful term of "effective coronary perfusion pressure" was introduced to express the difference between central aortic pressure and right atrial pressure: $ECPP = Ao_{pr} - RA_{pr}$. This simple concept has not received the clinical attention it deserves.

In addition to pericardial tamponade, a classic example of a condition in which central aortic pressure and cardiac output are falling at the same time that right atrial pressure is rising, there are a number of analogous clinical conditions. In congestive heart failure, ventricular end-diastolic pressure becomes elevated, forcing an increase in atrial pressure. As right atrial pressure rises due to congestive heart failure in any condition previously associated with a reduced central aortic pressure, the same reduction in effective coronary perfusion pressure occurs as in pericardial tamponade. This is seen in aortic stenosis, in which the central aortic pressure is at a fixed low

level, or during acute myocardial infarction, in which reduced central aortic pressure is a common problem early in the clinical course. In either of these conditions an elevation of right atrial pressure is quickly expressed as reduced effective coronary perfusion pressure, supporting the gravity of the appearance of congestive failure in these conditions.

Reduced effective coronary perfusion pressure due to a combination of right atrial hypertension plus aortic hypotension not only renders the entire myocardium more anoxic than does simple reduction of central aortic pressure alone, but in an area of myocardium previously ischemic due to focal coronary sclerosis this degree of further deprivation of oxygen may make the critical difference between survival or infarction.

An excellent example of sudden reduction in effective coronary perfusion pressure is seen in acute pulmonary embolism. The increase in pulmonary vascular resistance, much of which is reflex in origin, acts in two directions. It not only abruptly elevates the right ventricular and right atrial pressures, the latter elevation being compounded if the tricuspid valve becomes incompetent, but it also abruptly reduces the volume of blood traversing the pulmonary vascular bed to fill the left heart, thereby reducing cardiac output and central aortic pressure. Although there may be some reflex effect on coronary artery tone in acute pulmonary embolism, the commonly observed acute myocardial anoxia must be related more to the sudden reduction in coronary perfusion.

Chronic pulmonary hypertension of any etiology can produce a similar effect on coronary perfusion, and the refractoriness of congestive failure in the case of cor pulmonale may be due partially to this factor. Pulmonary hypertension and the resistance to normal blood flow into the left heart may be either at the level of the pulmonary arterioles or a stenotic mitral valve, or both. In all diseases with pulmonary hypertension the development of incompetence of the tricuspid valve is a critical event because it further elevates right atrial pressure and reduces effective coronary perfusion pressure. Chest pain which occurs in cases of pulmonary hypertension of any etiology[3] may well be due to myocardial ischemia so induced, a point previously suggested by Dresdale, Schultz and Michtom.[4]

It is likely that an acute rise in pulmonary arterial pressure (as in acute pulmonary embolism) is less well tolerated by patients with chronic pulmonary hypertension than by patients with previously normal pulmonary arterial pressures, because of the associated right ventricular hypertrophy in the former. A thick right ventricle which has already been generating pressure that approaches that in the central aorta leaves the patient less range of safety in regard to effective coronary perfusion pressure, especially if the right ventricle has been failing and the end-diastolic pressure is elevated, or if the tricuspid valve is incompetent. A patient with long-standing mitral stenosis, chronic pulmonary hypertension, and a hypertrophied right ventricle tolerates poorly any additional increase in pulmonary arterial pressure, and one of the important reasons is the effect on coronary perfusion. Whether a right ventricle of normal thickness dilates more easily during acute pulmonary hypertension and more often produces tricuspid valvular incompetence is conjectural, as is the possibly different effect that this might have on effective coronary perfusion pressure.

Any disease which restricts normal ventricular filling and consequently raises atrial pressure doubly reduces effective coronary perfusion pressure, because of combined right atrial hypertension and aortic hypotension. This applies not only to pericardial tamponade but also to constrictive pericarditis, subendocardial fibroelastosis, primary cardiac amyloidosis, and severe myocardial fibrosis (due to long-standing coronary sclerosis, or severe inflammation and repair, or hemachromatosis).

Gregg[1] has lucidly discussed the many complex factors which contribute to coronary blood flow, and has emphasized that the left ventricle furnishes not only the pressure head responsible for coronary artery filling, but also the major resistance to coronary filling during systole. Furthermore, the rate and volume of flow in the proximal coronary arteries, the distal coronary arteries, and the coronary veins are by no means parallel. Thus, phasic variation in an elevated right atrial pressure may produce a different effect on coronary emptying if the elevation is mainly in the *a* wave (as in tricuspid stenosis) or in the *v* wave (as in tricuspid regurgitation); whether one has a more deleterious effect than the other on coronary emptying has received little attention.

Therapeutically it is important to consider the roles of both right atrial pressure and central aortic pressure in states associated with reduced coronary flow. Phlebotomy for the venous hypertension of constrictive pericarditis may have catastrophic results, for, although it effectively reduces venous pressure, it simultaneously reduces blood volume, cardiac output, and central aortic pressure; thus, the salutary effect at the venous end of coronary flow may be neutralized and even overbalanced by the loss of perfusion pressure at the aortic end. The reverse was clearly shown in the studies of Binion and his colleagues,[2] when they produced improvement in coronary flow in pericardial tamponade by the administration of a systemic vasopressor agent (metaraminol).

Clinical conditions manifested by both right atrial hypertension and reduced central aortic pressure should have initial therapy directed at restoration and maintenance of central aortic pressure. This alone may sufficiently improve coronary flow so that myocardial efficiency returns and venous hypertension is reduced. In certain circumstances, such as congestive failure during acute myocardial infarction, it may be necessary to employ both administration of vasopressor agents and phlebotomy; in such cases a consideration of their influences on effective coronary perfusion pressure certainly indicates that efforts to elevate central aortic pressure should precede efforts to reduce right atrial pressure by phlebotomy.

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The Sturge-Weber syndrome

The literature abounds with reports of cases in which there are coexistent congenital vascular anomalies of the skin and of the central nervous system. The Sturge-Weber malady is the most frequently encountered of these, albeit a rare enough condition in individual clinical practice. A motley group of cases have been described under the title of Sturge-Weber disease, and Alexander and Norman,[1] in a recent concise monograph, put forward a plea for a more rigid definition of the disease, conforming to the original descriptions. It is insisted that the presence of a facial nevus and of angiomatosis at the leptomeningeal level are prerequisites for the diagnosis. If these criteria are accepted, a remarkably uniform clinical picture emerges. The angiomatosis on the surface of the brain is usually revealed by extensive deposits of cortical calcification, which as these authors show from the literature, and in one of their cases,[1] are rarely detectable radiologically before the age of about 2 years. The calcifications have a characteristic gyriform pattern, which, however, is not exclusively confined to the Sturge-Weber condition.

Several important deductions have been put forward.[1] It is noted that the nevus affects the supraocular part of the face in true Sturge-Weber disease, and an embryologic correlation is offered in explanation of this feature.

The histories indicate the frequency of a promising start in life, and even of intellectual precocity, shattered by the advent of epilepsy. Lobectomy, which has been practised since 1936 (Olivecrona[2]), should be considered in infancy before epilepsy has occurred, if the facial nevus has the requisite distribution, and if a small local exploration in the occipital or parietal regions of the brain reveals the typical meningeal vascular anomaly. In this manner, experience may reveal how far the epilepsy contributes to the serious intellectual retardation which is almost the rule in those cases.

Operation revealed a conspicuous cyanosis of the abnormal meningeal vessels in several cases.[1] It is interesting that there may be a parallel between the cardiac instability which results from the territorial anoxia of coronary occlusion and the cerebral instability which is manifest as epilepsy in Sturge-Weber disease.

Evidently in the more gross examples, with dense cortical calcification, the electrical activity shown in direct recordings from the exposed cortex is minimal, yet it is grossly dysrhythmic in the adjacent cortex of normal appearance. Removal of this electrically silent area may have a remarkable steadying effect on the tracing from the rest of the cerebrum, with substantial clinical benefit in sequence. The electrical "silence" may be due to retention of carbon dioxide in the calcified cortex underlying the abnormal vessels, and has an effect on the electroencephalogram similar to that observed when a main bronchus is clamped at operation (Wilson[3]).

Falconer and Rushworth[4] have recently described their encouraging experience with hemispherectomy in patients with Sturge-Weber syndrome who already had hemiparesis.

The recent suggestion by Hayward and Bower[5] that the chromosomal abnormality which they found in one case of Sturge-Weber disease may be a characteristic has not been confirmed in an investigation of Alexander and Norman's cases, nor by Lehmann and Forssman[6] in Sweden. No recorded examples of the true Sturge-Weber anomaly were found to occur twice in a family tree, nor was there any association with congenital heart disease.

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Letter to the Editor

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To the Editor:

We are writing on behalf of the University of Hue in the free Republic of Vietnam. The University, which opened its doors in 1957, has, in the three and a half years since that time, nearly doubled its enrollment, thereby justifying the faith of its founders that this new institution would fulfill a vital need in this crucial part of the free world.

Last fall the University expanded its activities by opening a school of medicine—the world's newest—to provide a full seven-year program of medical education in all fields: neurology, microbiology, nursing, public health, tropical medicine, etc.

As part of our program of assistance to the people and institutions of Vietnam, we have undertaken to obtain for the medical school certain books, professional journals and other resource materials, based on needs submitted to us by the medical staff of the Hue city hospital (which is being used by the University for its training program). Among the publications which the University has requested is the *American Heart Journal*. We would very much appreciate your bringing this fact to the attention of your readers, who may wish to dispose of back copies of the Journal in a worth-while manner. Such a gift would be an invaluable addition to the University's limited resources and would be further evidence of the community of feeling which exists among educators and publishers throughout the free world.

All donations may be sent to this office, where each will be catalogued and prepared for shipment to Vietnam. We should like to point out that gifts to the American Friends of Vietnam—including gifts of this nature—are deductible from taxable income; each donor will receive a formal receipt acknowledging the value of the contribution.

If there is any further information you would like, either about the University of Hue or about our own organization, please do not hesitate to get in touch with us.

Louis Andreatta
Executive Secretary
American Friends of Vietnam

Book reviews

MODERN TRENDS IN CARDIAC SURGERY. Edited by H.R.S. Harley, M.S., F.R.C.S., Consultant Thoracic Surgeon, United Cardiff Hospitals and Welsh Regional Hospital Board. New York, 1960, Paul B. Hoeber, Inc., 282 pages. Price $15.

This book by twenty-two British surgeons is an interesting expression of current British surgical practice in cardiac surgery. This book makes no attempt to exhaustively cover the entire field of cardiac surgery, but nonetheless a tremendous amount of information is available in its 282 pages. This book was edited by H.R.S. Harley, a Welsh thoracic surgeon, and the two chapters which he contributed on hemodynamic alterations in cardiac disease and on surgical treatment of mitral stenosis are especially informative. All of the chapters in this book are very easy to read. With just a little expansion this book could very easily be the outstanding text in the field of cardiac surgery.

A few definite deficiencies that exist are related primarily to the nature of the subject material itself and the rapid alterations that are taking place in this field at all times. For example, in the chapter on cardiac arrest there is no reference to the method of closed-chest massage, described by Kouwenhoven and certain to achieve widespread use. This is not an oversight, I am sure, but simply due to the fact that the book went to the printer before this information became available.

HEART SOUNDS AND MURMURS: A CLINICAL AND PHONOCARDIOGRAPHIC STUDY. By P. A. Ongley, Consultant in Pediatrics, Mayo Clinic, Rochester, Minn.; H. B. Sprague, Board of Consultation, Massachusetts General Hospital and Past President, American Heart Association; M. B. Rappaport, Former Head of Department of Electrophysiologic Research, Sanborn Company, Waltham, Mass.; A. S. Nadas, Cardiologist, Childrens Hospital, Boston, Mass. New York, 1960, Grune & Stratton, Inc., 360 pages. Price $9.75.

This book is divided into six sections: I. History and Physics; II. Heart Sounds and Murmurs; III. Diseases of the Heart Valves; IV. Rheumatic Heart Disease; V. Congenital Heart Disease; VI. Miscellaneous. As the titles imply, there is some repetition of content in the various sections.

Approximately the first one hundred pages of this small volume are devoted to the physics of sound and historical aspects as they relate to the development and application of auscultation and phonocardiography. As might be expected, much of this is based on previously published works of Rappaport and Sprague. The methods of phonocardiography which form the basis of the book are those advocated by these two investigators, in particular, the "logarithmic" and "stethoscopic" methods used in recording the heart sounds from the chest wall. Inadequate coverage is given to techniques and methods advocated by other authors, and published under such names as "calibrated phonocardiography," "filtered phonocardiography," "selective phonocardiography," "spectral phonocardiography," and "intracardiac, esophageal and tracheal phonocardiography." This lack of comprehensiveness in the coverage of methodology is not necessarily a defect, however, provided that the reader is somewhat familiar with the over-all phonocardiographic literature.

The other approximately two hundred and fifty pages of the book deal more specifically with the more "clinical" aspects of auscultation and phonocardiography. These sections excellently serve to transfer the recently accumulated wealth of research information dealing with cardiovascular sound into the realm of clinical application. Very few useful features in clinical auscultation have been omitted. Coverage is incomplete, however, in certain areas, namely, pericardial friction rubs, extracardiac sounds, and a few of the finer aspects of auscultation in congenital heart disease.

In general, this book is recommended for those interested in auscultation and phonocardiography. The presentation is fairly well organized. The paper and printing are excellent, the illustrations are good, and the indexing is satisfactory.

CLINICAL DISTURBANCES OF RENAL FUNCTION. By Abraham G. White, M.D., F.A.C.P., Associate Visiting Physician and Chief of the Renal Disease Clinic, Queens Hospital Center, Jamaica, N. Y. Philadelphia and London, 1961, W. B. Saunders Company, 468 pages. Price $10.50.

This book is meant for the practicing physician facing clinical problems in which there is disturbance of kidney function. There are sixteen chapters, with such titles as "Acute Renal Failure," "Obstetric Aspects of Renal Function," and "Surgical Aspects of Renal Function." Each subject is discussed from the point of view of pathogenesis, relationship of clinical features to disturbed function, and the logical therapy. The discussion is very readable, and at all times the author is at pains to avoid being dogmatic. The reasons underlying the methods of therapy are given, and the evidence available to support the reasons is indicated. In order to keep the text simple, references only to major works or reviews are given, and the bibliography is short. In general, the opinions expressed conform to the prevailing opinion of modern renal workers. For all of this, the book cannot but be praised. More questionable is the selection of subjects that have been included in this book. Sections on the various endocrine diseases, hepatic cirrhosis, and the principles of genetics hardly seem necessary.

Inevitably, some criticism can be made of individual parts of the book, such as the omission of mention of the use of anabolic steroids in the management of acute renal failure, although the

case for them in patients with disturbances of pregnancy is strong; and whereas the importance of differentiating dehydration oliguria from acute tubular necrosis is repeatedly stressed, no real help is given on how to do it (such as urine urea concentrations or urine specific gravities). Another fault is the system of cross references, giving chapter numbers only, which is a poor one.

The book is a good one, and, in addition to the practicing physician to whom it is directed, should provide helpful reading to medical students and others who are interested in renal problems.

Announcements

A COURSE IN INTERPRETATION OF COMPLEX ARRHYTHMIAS will be given at Michael Reese Hospital by Louis N. Katz, M.D., Richard Langendorf, M.D., and Alfred Pick, M.D. This is an *advanced* course intended only for experienced electrocardiographers. The class will meet daily from 9:00 A.M. to 5:00 P.M., Dec. 4-8, 1961.

Further information and a copy of the lecture schedule may be obtained from Miss Beverley Petzold, Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital and Medical Center, Chicago 16, Ill.

The Joint Annual and Scientific Meetings of the CANADIAN HEART ASSOCIATION and the NATIONAL HEART FOUNDATION OF CANADA will be held in Vancouver, B.C., Nov. 13-18, 1961.

Address enquiries to Dr. John B. Armstrong, National Heart Foundation of Canada, 501 Yonge St., Toronto 5, Canada.

Final plans have been announced for the ELEVENTH ANNUAL INSTRUMENT SYMPOSIUM AND RESEARCH EQUIPMENT EXHIBIT to be held Oct. 9-12 and Oct. 10-13, 1961, respectively, at the National Institutes of Health, Bethesda, Md.

Under the auspices of the local sections of six national professional societies, more than 20 scientists actively engaged in research in their specialties will report on recent developments in research methods and instrumentation.

At the research equipment exhibit, 121 of the nation's leading manufacturers of electronic, mechanical, and optical instruments for laboratory and clinical research will display a wide array of the latest scientific apparatus.

This year's symposium will consist of seven sessions. Dr. Alton Meister, Chairman of the Department of Biochemistry, Tufts University School of Medicine, will preside over the opening session dealing with applied gas chromatography. Other topics on the 4-day scientific program are: factors influencing the interpretation of infrared spectra, optical rotatory dispersion, thermogravimetric analysis, electron-probe analysis, the application of physiologic instrumentation to clinical problems, and electron magnetic resonance. Chairmen of the discussion sessions include Dr. Ellis R. Lippincott, University of Maryland; Dr. Ulrich Weiss, National Institute of Arthritis and Metabolic Diseases; Dr. Saul Gordon, Fairleigh Dickinson University; Dr. Isidore Adler, U. S. Geological Survey; Gerald S. Cohen, Division of Research Services, N.I.H.; and Dr. Edwin D. Becker, National Institute of Arthritis and Metabolic Diseases.

Dr. James A. Shannon, Director of N.I.H., will welcome symposium participants at the opening meeting, October 9, at 8:00 P.M. Scientific sessions will continue through the week with two meetings daily, at 2:00 P.M. and 8:00 P.M. The closing session will be held October 12, at 2:00 P.M.

The research equipment exhibit will be open daily from 11:00 A.M. to 5:00 P.M., October 10-13. On October 11, the exhibit will remain open until 9:00 P.M.

Six of the exhibiting firms will hold special instrumentation clinics to demonstrate the research applicability of their newest equipment. Instruments shown will include an electronic spectrophotometer, refrigerated cell fractionator, atomic absorption analyzer, immunoelectrophoresis accessories, electronic hematocrit, and a protein monitor. Demonstrations will be given October 11, 12, and 13 from 9:30 to 10:15 A.M. and 10:15 to 11:00 A.M.

For additional information, write or call James B. Davis, National Institutes of Health, Public Health Service, Bethesda 14, Md. Phone: OLiver 6-4000, Ext. 2315.

THE AMERICAN UROLOGICAL ASSOCIATION offers an ANNUAL AWARD of $1,000 (first prize of $500, second prize of $300, and third prize of $200) for essays on the result of some clinical or laboratory research in urology. Competition is limited to urologists who have been graduated not more than ten years, and to hospital interns and residents doing clinical or laboratory research work in urology. Animal research is not necessary.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Bellevue-Stratford Hotel, Philadelphia, Pa., May 14-17, 1962.

For full particulars write to the Executive Secretary, William P. Didusch, 1120 North Charles St., Baltimore 1, Md. Essays must be in his hands before Nov. 15, 1961.